THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application & Provisional Specification of the extract of Patent Application No.862/CHE/2003, dated 28/10/2003 by Dr. Reddy's Laboratories Limited having its registered office at 7-1-27, Ameerpet, Hyderabad - 500 016, Andhra Pradesh, INDIA.

IB/04/3429

.....In witness thereof

I have hereunto set my hand

Dated this the 9th day of November 2004

M.S. Venkataraman

(M.S. VENKATARAMAN)
Assistant Controller of Patents & Designs

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 4th Floor, Annex.II
No.443, Anna Salai, Teynampet, Chennai – 600 018

Received Rs 3000/- in Cash
Cheque/M.O./P.O/D.D/on 28-X-03
Vide C.B.R. No. 6846

25/X

FORM 1
THE PATENTS ACT, 1970
APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7and Rule 33A)

We, Dr. Reddy's Laboratories Ltd., an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016 hereby declare

1. (a) that we are in possession of an invention titled **"NOVEL COMPOUNDS AND THEIR USE IN MEDICINE, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"**
   (b) that the provisional specification relating to this invention is filed with this application.
   (c) that there is no lawful ground of objection to the grant of a patent to us.
2. further declare that the inventors for the said invention are DEBNATH BHUNIYA, GURRAM RANGA MADHAVAN, SAIBAL KUMAR DAS, JAVED IQBAL, RANJAN CHAKRABARTI AND LABANYAMOY KOLE All citizens & residents of India belonging to Dr. REDDY'S LABORATORIES LTD., 7-1-27, AMEERPET, HYDERABAD - 500 016.
3. that we are the assignee of the true and first inventors
4. that our address for service in India is as follows;

   Head,
   Intellectual Property Management,
   Discovery Research,
   Dr. Reddy's Laboratories Ltd.,
   Bollaram Road, Miyapur,
   Hyderabad-500049, ANDHRA PRADESH

5. We, the true and first inventors for this invention declare that the applicant herein is our assignee

(Signed) Debnath Bhuniya
DEBNATH BHUNIYA

(Signed) Gurdhavan
GURRAM RANGA MADHAVAN

(Signed) Saibal Kumar Das
SAIBAL KUMAR DAS

(Signed) Javed Iqbal
JAVED IQBAL

(Signed) Ranjan Chakrabarti
RANJAN CHAKRABARTI

(Signed) Labanyamoy Kole
LABANYAMOY KOLE

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application
7. following are the attachments with the application

ORIGINAL 28 OCT 2003 0622/CHE/2003

(a) provisional specification including FORM 2 (100 pages, in duplicate)
(b) fee Rs. 3000.00 (three thousand rupees only) cheque bearing No. 964471 dated, 09.10.2003, drawn on bank payable at Chennai.

We request that a patent may be granted to us for the said invention

Dated this twenty first (21st) day of October 2003

(Signed)
Dr. R. Rajagopalan
for Dr. Reddy's Laboratories Ltd.

To,
The Controller of Patents
The Patents Office Branch, Chennai.

FORM 2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION

(SECTION 10)

NOVEL COMPOUNDS AND THEIR USE IN MEDICINE, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Dr. Reddy's Laboratories Limited,
an Indian Company having its registered office at
7-1-27, Ameerpet
Hyderabad - 500 016, Andhra Pradesh, India

THE FOLLOWING SPECIFICATION DESCRIBES THE NATURE OF THE INVENTION

Field of the Invention

The present invention relates to the compounds of formula 1 and their physiologically tolerable salts. The present invention also relates to a process for the preparation of compounds of formula 1, to pharmaceutical compositions containing compounds of formula 1 and their use as medicament, in particular as antidiabetic, hypolipidemic, antiobesity and hypocholesterolemic agents.

The compounds of the present invention lower plasma glucose, triglycerides, lower total cholesterol (TC) and increase high density lipoprotein (HDL) and decrease low density lipoprotein (LDL), which have a beneficial effect on coronary heart disease and atherosclerosis.

The compounds of general formula (I) are useful in reducing body weight and for the treatment and/or prophylaxis of diseases such as atherosclerosis, stroke, peripheral vascular diseases and related disorders. These compounds are useful for the treatment of hyperlipidemia, hyperglycemia, hypercholesterolemia, lowering of atherogenic lipoproteins, VLDL (very low density lipoprotein) and LDL. The compounds of the present invention can be used for the treatment of renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis and nephropathy. The compounds of general formula (I) are also useful for the treatment and/or prophylaxis of leptin resistance, impaired glucose tolerance, disorders related to syndrome X such as hypertension, obesity, insulin resistance, coronary heart disease and other cardiovascular disorders. These compounds may also be useful as aldose reductase inhibitors, for improving cognitive functions in dementia, treating diabetic complications, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, arteriosclerosis, retinopathy, xanthoma, eating disorders, inflammation and for the treatment of cancer. The compounds of the present invention are also useful in the treatment and/or prophylaxis of the above said diseases in combination/concomittant with one or more HMG CoA reductase inhibitor; cholesterol absorption inhibitor; antiobesity drug; lipoprotein disorder treatment drug; hypoglycemic agent: insulin; biguanide; sulfonylurea; thiazolidinedione; dual PPARα and γ or a mixture thereof.

Description of related art

Atherosclerosis and other peripheral vascular diseases affect the quality of life of millions of people. Therefore, considerable attention has been directed towards understanding the etiology of hypercholesterolemia and hyperlipidemia and development of effective therapeutic strategies.

Hypercholesterolemia has been defined as plasma cholesterol level that exceeds arbitrarily defined value called "normal" level. Recently, it has been accepted that "ideal" plasma levels of cholesterol are much below the "normal" level of cholesterol in the general population and the risk of coronary artery disease (CAD) increases as cholesterol level rises above the "optimum" (or "ideal") value. There is clearly a definite cause and effect-relationship between hypercholesterolemia and CAD, particularly for individuals with multiple risk factors. Most of the cholesterol is present in the esterified forms with various lipoproteins such as Low density lipoprotein (LDL), Intermediate density lipoprotein (IDL), High density lipoprotein (HDL) and partially as Very low density lipoprotein (VLDL). Studies clearly indicate that there is an inverse correlationship between CAD and atherosclerosis with serum HDL-cholesterol concentrations (Stampfer *et al., N. Engl. J. Med.,* 325 (1991), 373-381). The risk of CAD increases with increasing levels of LDL and VLDL.

In CAD, generally "fatty streaks" in carotid, coronary and cerebral arteries, are found which are primarily free and esterified cholesterol. Miller *et al., (Br. Med. J.,* 282 (1981), 1741-1744) have shown that increase in HDL-particles may decrease the number of sites of stenosis in coronary arteries of human, and high level of HDL-cholesterol may protect against the progression of atherosclerosis. Picardo *et al., Arteriosclerosis* 6 (1986) 434-441 have shown by *in vitro* experiment that HDL is capable of removing cholesterol from cells. They suggest that HDL may deplete tissues of excess free cholesterol and transfer it to liver, which is known as reverse cholesterol transport, (Macikinnon *et al., J. Biol. chem.* 261 (1986), 2548-2552). Therefore, agents that increase HDL cholesterol would have therapeutic significance for the treatment of hypercholesterolemia and coronary heart diseases (CHD).

Obesity is a disease highly prevalent in affluent societies and in the developing world and is a major cause of morbidity and mortality. It is a state of excess body fat accumulation. The causes of obesity are unclear. It is believed to be of genetic origin or promoted by an interaction between the genotype and environment. Irrespective of

the cause, the result is fat deposition due to imbalance between the energy intake versus energy expenditure. Dieting, exercise and appetite suppression have been a part of obesity treatment. There is a need for efficient therapy to fight this disease since it may lead to coronary heart disease, diabetes, stroke, hyperlipidemia, gout, osteoarthritis, reduced fertility and many other psychological and social problems.

Diabetes and/or insulin resistance is yet another disease which severely effects the quality of large population in the world. Insulin resistance is the diminished ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistance, the body secretes abnormally high amounts of insulin to compensate for this defect; failing which, the plasma glucose concentration inevitably raises and develops into diabetes. Among the developed countries, diabetes mellitus is a common problem and is associated with a variety of abnormalities including obesity, hypertension, hyperlipidemia (*J. Clin. Invest.*, 75 (1985) 809-817; *N. Engl. J. Med* 317 (1987) 350-357; *J. Clin. Endocrinol. Metab.*, 66 (1988) 580-583; *J. Clin. Invest.*, 68 (1975) 957 - 969) and other renal complications (patent publication No. WO 95/21608). It is now increasingly being recognized that insulin resistance and relative hyperinsulinemia have a contributory role in obesity, hypertension, atherosclerosis and type 2 diabetes mellitus. The association of insulin resistance with obesity, hypertension and angina has been described as a syndrome having insulin resistance as the central pathogenic link-Syndrome-X.

Hyperlipidemia is the primary cause for cardiovascular (CVD) and other peripheral vascular diseases. High risk of CVD is related to the higher LDL (Low Density Lipoprotein) and VLDL (Very Low Density Lipoprotein) seen in hyperlipidemia. Patients having glucose intolerance/insulin resistance in addition to hyperlipidemia have higher risk of CVD. Numerous studies in the past have shown that lowering of plasma triglycerides and total cholesterol, in particular LDL and VLDL and increasing HDL cholesterol help in preventing cardiovascular diseases. Peroxisome Proliferator Activated Receptors (PPARs) are orphan receptors belonging to the steroid/retinoid receptor super family of ligand activated transcription factors. (Wilson T. M. and Wahli W., Curr. Opin. Chem. Biol., 1997, Vol. 1, 235-241). Three mammalian Peroxisome Proliferator Activated Receptors (PPARs) have been isolated and termed PPAR-α, PPAR-γ and PPAR-δ. These PPARs regulate expression of target genes by binding to DNA sequence elements.

Certain compounds that activate or otherwise interact with one or more of the PPARs have been implicated in the regulation of triglyceride and cholesterol levels in animal models. (U.S. patents 5,847,008; 5,859,051 and PCT publications WO 97/28149; WO 99/04815.

Wealth of information exists on the influence of PPAR α agonists on the cardiovascular risk profile for example fibrate class of compounds which are weak PPAR-α agonists correct atherogenic dyslipoproteinemia. Several angiographic intervention trials have demonstrated a beneficial action of these drugs on atherosclerotic lesion progression and results from primary and secondary prevention trials show a decreased incidence of cardiovascular events. (Ricote M. and Glass C. K.; Trends in Pharmacological Sciences; 2001; 22(9); 441-443.

Despite the fact that fibrates, which are weak PPAR-α activators, reduce the plasma triglyceride levels and elevate the levels of HDL-C simultaneously, they are not the drugs of choice, because of: low efficacy requiring high doses, incidence of Myositis and contra-indicated in patients with impaired renal and hepatic function and to pregnant and nursing women.

However there has been rapid progress in our understanding on the role of PPAR-α in different pathophysiological conditions in addition to the well-documented favourable effects on lipid profile. The inflammatory activation of aortic smooth muscle cells, which is the hallmark of atherosclerosis, seems to be inhibited by the enhanced PPAR-α activity. (Vamecq J. and Latruffe N; Lancet; 1999; 354; 141-148)

Recent evidence suggests the role of PPAR-α receptors in improving insulin sensitivity. It has been demonsrated that by lowering circulatory and muscle lipids in insulin-resistant rodent models such as obese Zuker rats, high fat-fed mice and sucrose-lard fed rats, PPAR-α ligands improve insulin sensitivity and obesity. Further the lipid lowering activity of the statins has been linked to a cross talk with PPAR-α receptor in addition to limited cholesterol availability. Some clinical trials have shown improvement in insulin sensitivity indices, wherein fibrates were employed. (i. Guerre-Millo M, Rounalt C. and Poulain P; Diabetes; 2001; 50; 2809-2814, ii. Muoio D. M., Way J. M. and Tanner C. J.; Diabetes; 2002; 51; 901-909, iii. Ye J, Doyle P. J.

and Iglesias M. A.; Diabetes; 2001; 50; 411-417, iv. Roglans N, Sanguino E. and Peris C; JPET; 2002; 302; 232-239.

Thus there is an interesting evidence for PPAR-α agonists to be used for lipid control and as per recent evidence even for insulin resistance. Limitations of the currently available medications coupled with the fact that lipid abnormalities are on the rise world over necessitate the discovery of more potent and safer PPAR-α agonists. In continuation of our research work on PPAR agonists (U.S. Patents 5,885,997; 6,054,453; 6,265,401: PCT application PCT/IB02/04275) to address this unmet need, a series of compounds have been synthesized which has been disclosed in the present invention.

The patent application WO 98/31359 describes substituted aromatic or non aromatic ring systems as vitronectin receptor antagonists. GB 2202223 describes sulfonylcarboxamides for the treatment of leukotriene-mediated naso-bronchial obstructive airpassageway conditions. US patent 600117 and 6399620 describes imino derivatives as vitronectin receptor antagonists and also as inhibitors of bone resorption. GB 2310669 describes substituted aromatic or non aromatic ring systems as a liquid crystalline medium. WO 92/01675 describes substituted bicyclic bis-aryl compounds which exhibit selective leukotriene B_4 antagonist activity. WO 01/53257 describes substituted pyrrole derivatives having hypolipedemic, hypocholesteremic activities.

Summary of the Invention

One object of the present invention is to provide compounds their pharmacologically tolerable salts capable of being used as antidiabetic, hypolipidemic, antiobesity and hypocholesterolemic agent.

Another object of the present invention is to provide methods for the production of the compounds of the present invention. Still another object of the present invention is to provide a pharmaceutical preparation which includes the compound of the present invention. Still another object of the present invention is to provide methods for the treatment of the conditions described above.

In accomplishing the above mentioned objects, there has been provided according to one aspect of the present invention, compounds of formula 1

Ar-I——Y——Ar-II——Z (1)

wherein Ar-I represents a monocyclic or polycyclic aromatic or non aromatic ring or partly saturated aromatic polycyclic, which may optionally contain up to 3 heteroatoms selected from N, S, or O. The said monocyclic or polycyclic ring may be unsubstituted or have up to 4 substituents which may be identical or different;

Ar-II represents a monocyclic or bicylic or partly saturated aromatic bicyclic aromatic ring which may optionally contain upto 3 heteroatoms selected from N, S or O. The aromatic ring may be unsubstituted or have up to 4 substituents which may be identical or different;

Z represents $(CH_2)oACR^7R^8(CH_2)_pW$, where o and p are each independently an integer from 0 to 4;

A represents O, S, NR^1 or a direct bond;

W represents CO_2R^9 or $CONR^1R^2$;

The substituents on Ar-I and Ar-II are selected from halogen, C_{1-10} alkyl, hydroxy, hydroxy C_{1-6} alkyl, C_{1-10} alkoxy, nitro, cyano, oxo, aryl, arylalkyl, alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, aryloxy, arylalkoxy, alkylcarbonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, arylalkoxycarbonylamino, fluorenylmethoxycarbonyl (Fmoc), fluorenylmethoxycarbonylamino (N-Fmoc), $-NR^1R^2$, $-OCONR^1R^2$, NR^1COOR^2, $-NR^1COR^2$, $-NR^1SO_2R^2$, $NR^1CONR^1R^2$, $-NR^2CSNR^1R^2$, SO_2R^3, OSO_2R^3, SO_2OR^3, $-SOR^3$, $-SO_2NR^1R^2$, $-COOR^4$, $-COR^4$, $-CONR^1R^2$, C_{1-10} alkylthio, thio C_{1-10} alkyl;

Y is selected from $(CH_2)_m$, $(CH_2)_mB(CH_2)_n$, $(CH_2)_mC(O)NR^5(CH_2)_n$, $(CH_2)_mNR^5C(O)(CH_2)_n$, $(CH_2)_mNR^5C(O)NR^5(CH_2)_n$, $(CH_2)_mNR^5C(O)O(CH_2)_n$, $(CH_2)_mNR^5C(O)(CH_2)_nO$, $(CH_2)_mNR^5OC(O)(CH_2)_n$, $(CH_2)_mCR^5CR^6(CH_2)_n$, $(CH_2)_mCR^5{=}CR^6(CH_2)_n$, $(CH_2)_mCR^5{\equiv}CR^6(CH_2)_n$, $(CH_2)_mOC(O)(CH_2)_n$, $(CH_2)_mC(O)O(CH_2)_n$, $(CH_2)_lB(CH_2)_mB(CH_2)_n$, where m and n are each independently an integer from 0 to 4; B may identical or different and represent S, O or NR^5 with a proviso that when Y has more than one heteroatom, no two heteroatoms are adjacent to each other.

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are each independently selected from hydrogen, halogen, hydroxy, hydroxy C_{1-10}alkyl, C_{1-10}alkyl, aryl, aroyl, aryl C_{1-10}alkyl, amino, amino C_{1-10} alkyl, acylamino, acylaminoC_{1-10}alkyl, C_{1-10}alkoxy, C_{1-10}alkoxyC_{1-10}alkyl, cycloalkyl, heterocyclyl, C_{1-10}alkoxycarbonyl, aryloxycarbonyl, C_{1-}

$_{10}$alkylaminocarbonyl, arylaminocarbonyl groups; optionally, either of R^8 or R^9 may form a bond with Ar-II.

in all their stereoisomeric forms and mixtures thereof in any ratio and pharmaceutically acceptable salts thereof;

According to an embodiment of the present invention, there is provided a compound wherein

Ar-I represents a monocyclic aromatic or non aromatic ring optionally containing up to 3 heteroatoms selected from N, S or O or C_{8-14} bicyclic aromatic or non aromatic or partly saturated aromatic bicyclic ring, which may optionally contain up to 3 heteroatoms selected from N, S or O. The said monocyclic or bicyclic ring may be unsubstituted or have up to 3 substituents which may be identical or different;

Ar-II represents a monocyclic or bicylic aromatic or partly saturated aromatic bicyclic ring which may optionally contain upto 3 heteroatoms selected from N or O. The aromatic ring may be unsubstituted or have up to 3 substituents which may be identical or different;

Y is selected from $(CH_2)_m$, $(CH_2)_mB(CH_2)_n$, $(CH_2)_mC(O)NR^5(CH_2)_n$, $(CH_2)_mNR^5C(O)(CH_2)_n$, $(CH_2)_mNR^5C(O)O(CH_2)_n$, $(CH_2)_mNR^5OC(O)(CH_2)_n$, $(CH_2)_mNR^5C(O)(CH_2)_nO$, $(CH_2)_mCR^5CR^6(CH_2)_n$, $(CH_2)_mCR^5{=}CR^6(CH_2)_n$, $(CH_2)_mCR^5{\equiv}CR^6(CH_2)_n$, $(CH_2)_mOC(O)(CH_2)_n$, $(CH_2)_mC(O)O(CH_2)_n$, $(CH_2)_lB(CH_2)_mB(CH_2)_n$, where l, m and n are each independently an integer from 0 to 4;

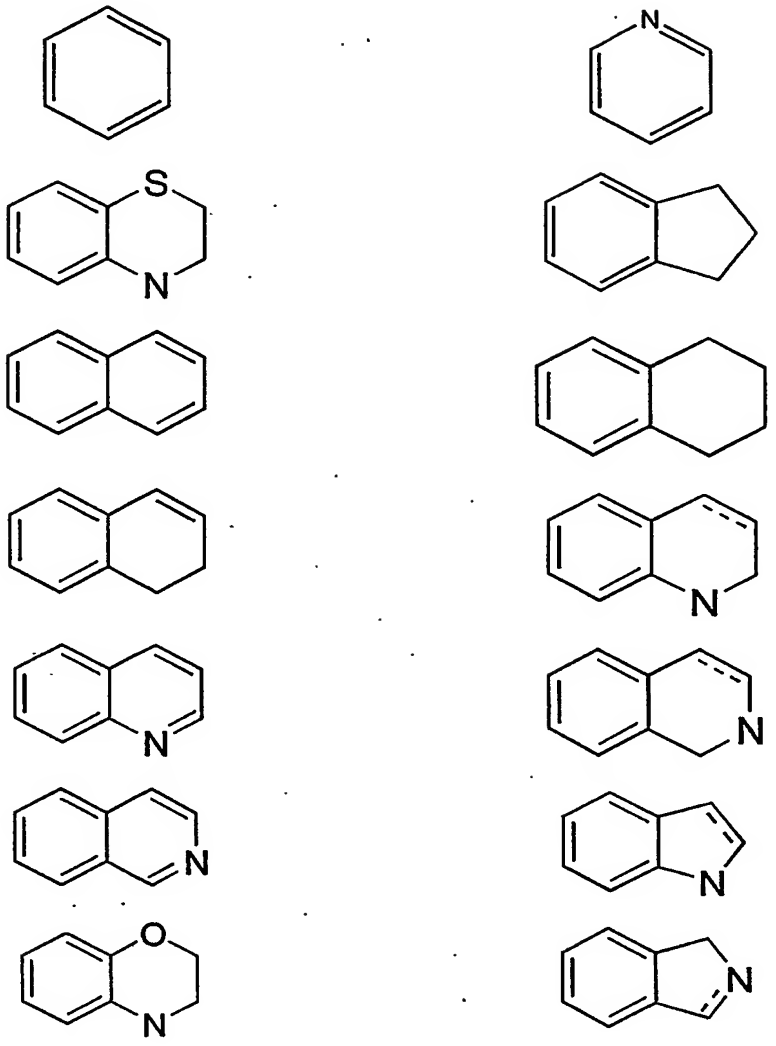
The substituents on Ar-I and Ar-II are selected from halogen, C_{1-10} alkyl, hydroxy, hydroxy C_{1-6} alkyl, C_{1-10} alkoxy, nitro, cyano, oxo, aryl, arylalkyl, aryloxy, arylalkyloxy, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, arylalkoxycarbonylamino, $-NR^1R^2$, $-OCONR^1R^2$, NR^1COOR^2, $-NR^1COR^2$, $-NR^1SO_2R^2$, $NR^1CONR^1R^2$, $-NR^2CSNR^1R^2$, SO_2R^3, SO_2OR^3,OSO_2R^3, SO_2OR^3, $-SOR^3$, $-SO_2NR^1R^2$, $-COOR^4$, $-COR^4$, $-CONR^1R^2$, C_{1-6} alkylthio, thioC_{1-6} alkyl;

A, B, W, Z, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 is as defined above.

in all their stereoisomeric forms and mixtures thereof in any ratio and pharmaceutically acceptable salts thereof;

According to another embodiment of the present invention, there is provided a compound wherein

Ar-I represents ring systems selected from



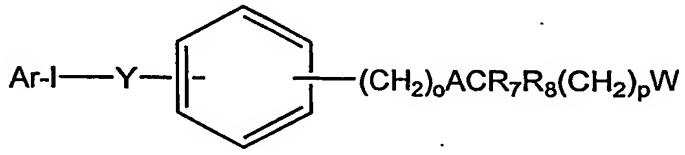
The said monocyclic or bicyclic systems may be attached to Y through either C or N through any of the rings.

Ar-II represents a monocyclic aromatic ring which may optionally contain upto 2 nitrogen. The aromatic ring may be unsubstituted or have up to 2 substituents which may be identical or different;

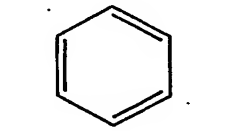
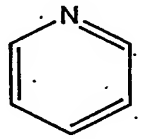
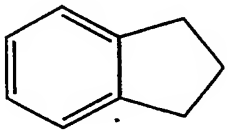
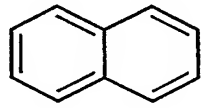
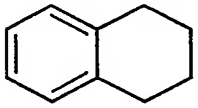
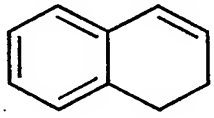
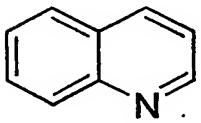
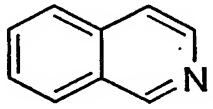
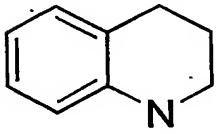
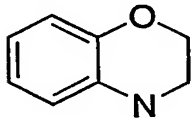
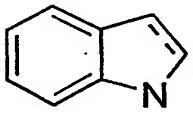
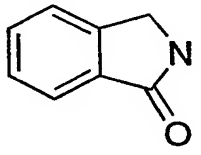
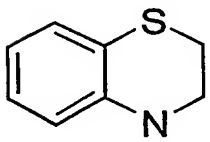
W, X, Y, Z, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 is as defined above.

in all their stereoisomeric forms and mixtures thereof in any ratio and pharmaceutically acceptable salts thereof;

According to a subclass of the present invention, there is provided a compound of the formula:



wherein Ar-I is selected from

Ar-I may be attached to Y through either C or N through any of the rings.

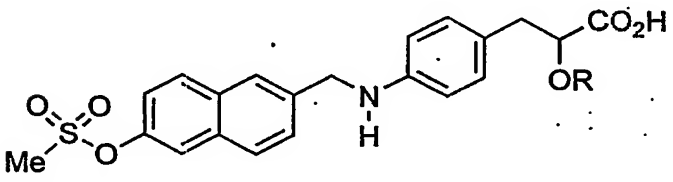
Y is selected from $(CH_2)_m$, $(CH_2)_mB(CH_2)_n$, $(CH_2)_mC(O)NR^5(CH_2)_n$, $(CH_2)_mNR^5C(O)(CH_2)_n$, $(CH_2)_mNR^5C(O)(CH_2)_nO$, $(CH_2)_lB(CH_2)_mB(CH_2)_n$

A represents a bond or O or NR^1

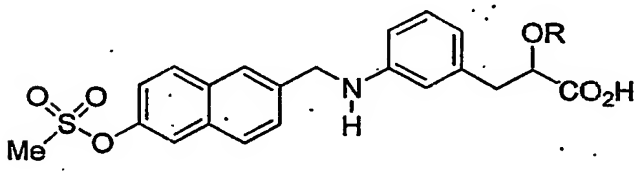
and all other variables are as defined earlier

in all their stereoisomeric forms and mixtures thereof in any ratio and pharmaceutically acceptable salts thereof;

The invention described in the above embodiments is exemplified by the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.



R = CH_3, CH_2CH_3



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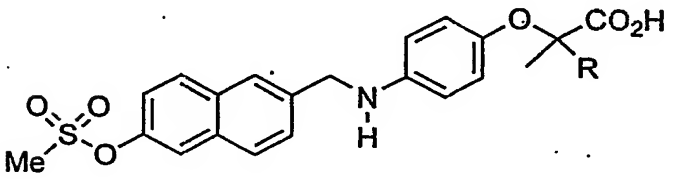

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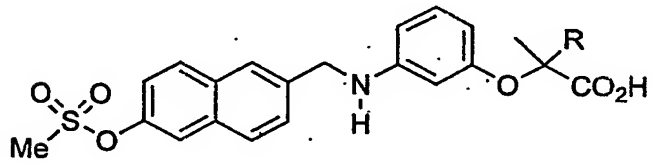
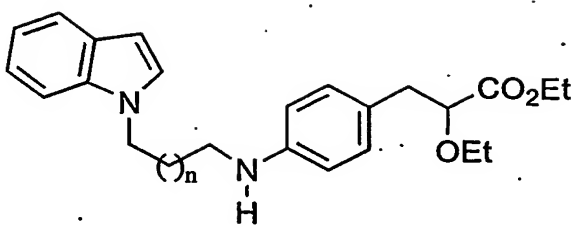
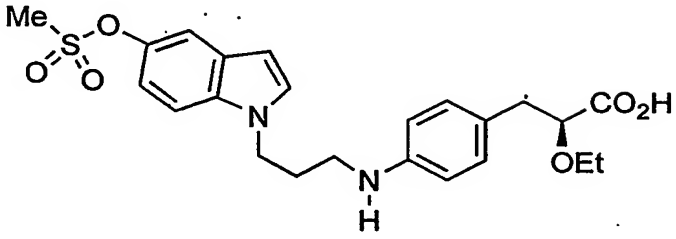
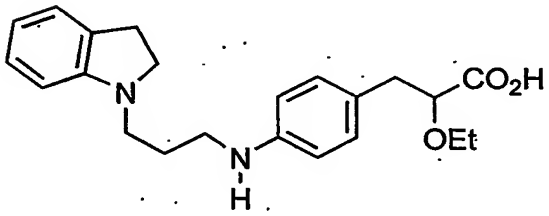


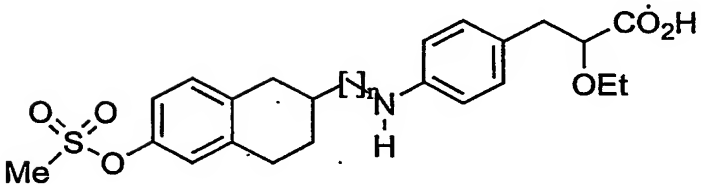
R = CH_3, CH_2CH_3


CO2Et
OEt
n
N
H

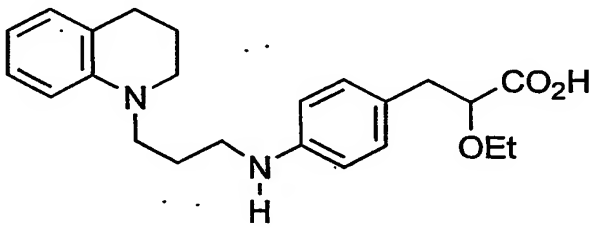
n = 1 or 2

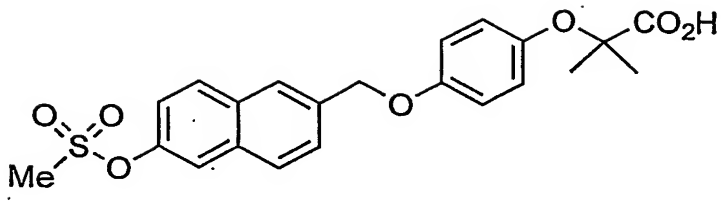

Me
S
O
O
O
CO2H
OEt
N
H

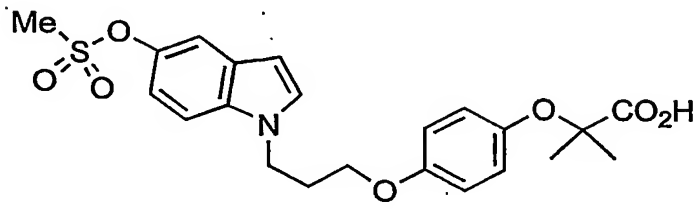

CO2H
OEt
N
H

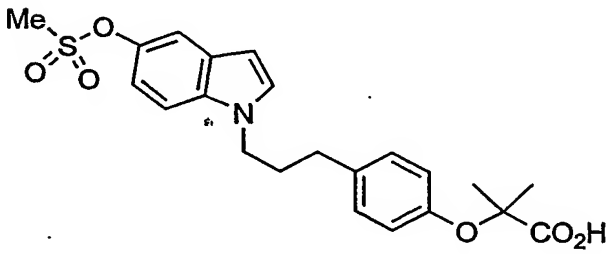

CO2H
OEt
n
N
H
O
S
O
Me

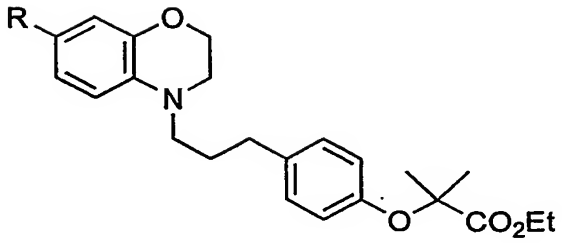
n = 1-3


CO2H
OEt
N
H

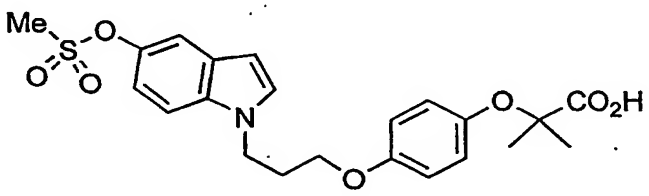


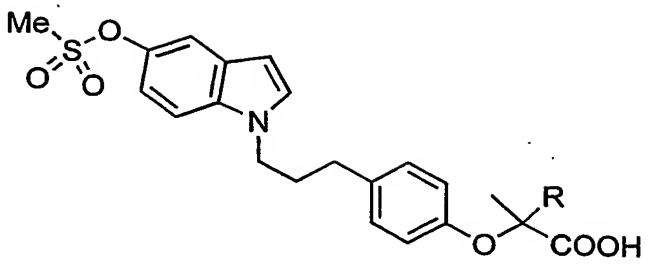




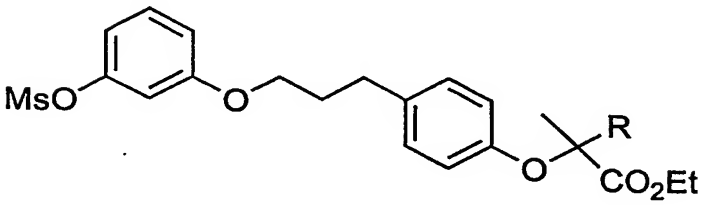


$R = H, OSO_2CH_3$

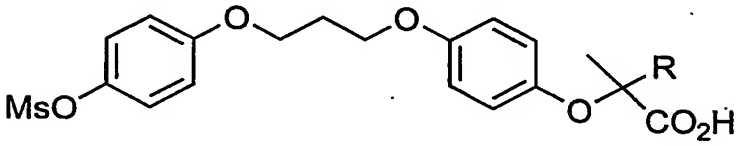




R = CH_3, CH_2CH_3



R = CH_3, CH_2CH_3



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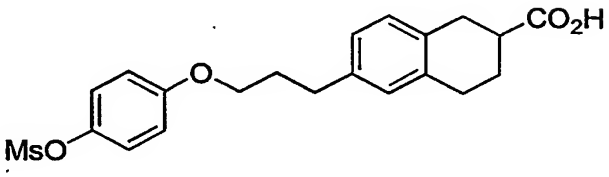
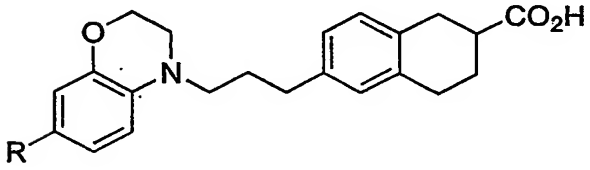
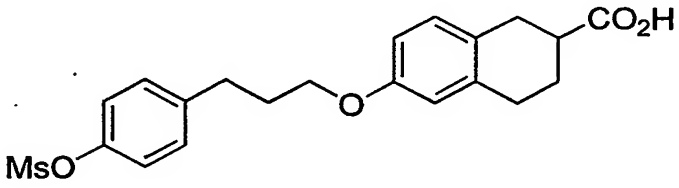
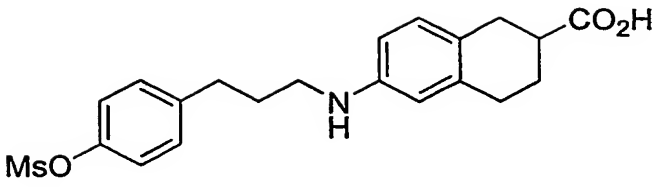
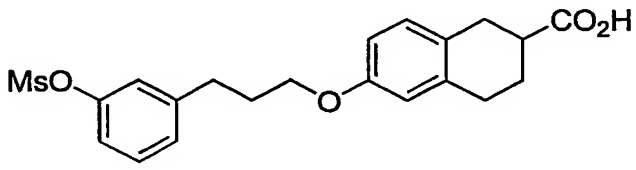


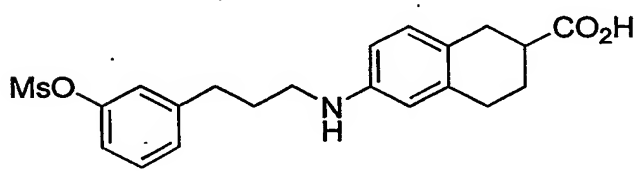


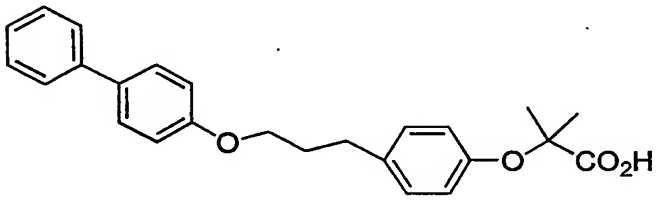
R = H, OSO_2CH_3

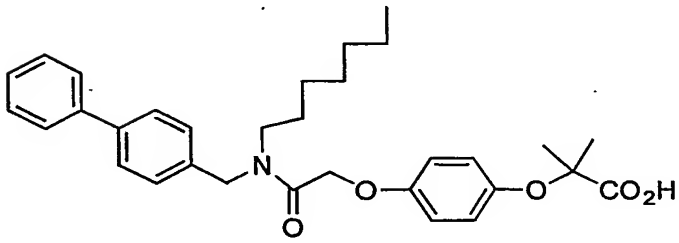












and pharmaceutically acceptable salts thereof

Further exemplifying the invention is a pharmaceutical composition comprising any of the compounds described above and a pharmaceutically acceptable carrier. Another illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

Further illustrating the invention is method for treatment and / or prophylaxis of a condition that requires an agonist of peroxisome proliferator activated receptor in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of any of the compounds described above. Preferably the condition is selected from insulin resistance and dyslipidemia such as diabetes, hypertension, coronary heart disease, atherosclerosis, stroke, peripheral vascular diseases, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, retinopathy, arteriosclerosis, xanthoma and related disorders.

Another illustration of the invention is method for treatment and / or prophylaxis of the above mentioned diseases using the compounds of the present invention in combination / concomitant with one or more HMG CoA reductase inhibitor; cholesterol absorption inhibitor; antiobesity drug; lipoprotein disorder treatment drug; hypoglycemic agents: insulin; biguanide; sulfonylurea; thiazolidinedione; dual PPARα and γ or a mixture thereof. The compounds of the present invention in combination with HMG CoA reductase inhibitor, cholesterol absorption inhibitor, antiobesity drug, hypoglycemic agent can be administered together or within such a period to act synergistically.

Further exemplifying the invention is a pharmaceutical composition, containing the compounds the present invention as defined above, their pharmaceutically acceptable salts or their pharmaceutically acceptable solvates and one or more HMG CoA reductase inhibitor; cholesterol absorption inhibitor; antiobesity drug; lipoprotein disorder treatment drug; hypoglycemic agents: insulin; biguanide; sulfonylurea; thiazolidinedione; dual PPARα and γ or a mixture thereof in combination with the usual pharmaceutically employed carriers, diluents and the like.

Detailed description of the embodiments

Compounds of the present invention are agonists or peroxisome proliferators activated receptor (PPAR) and hence are useful for the treatment or prophylaxis of patients suffering from a condition caused by the non activation of PPAR, who are in need of such therapy. Pharmacologically effective amounts of the compounds, including pharmaceutically acceptable salts thereof, are administered to the patient to inhibit insulin resistance and dyslipidemia such as diabetes, hypertension, coronary

heart disease, atherosclerosis, stroke, peripheral vascular diseases, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, retinopathy, arteriosclerosis, xanthoma and related disorders.

The compounds of the present invention are administered in dosages effective to agonize peroxisome proliferators activated receptor where such treatment is needed, as, for example, in the prevention or treatment of diabetes, hypertension, coronary heart disease, atherosclerosis, stroke, peripheral vascular diseases, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, retinopathy, arteriosclerosis, xanthoma and related disorders. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base. Representative salts include the following:

Li, Na, K, Ca, Mg, Fe, Cu, Zn, Mn; N,N'-diacetylethylenediamine, betaine, caffeine, 2-diethylaminoethanol, 2-dimethylaminoethanol, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, hydrabamine, isopropylamine, methylglucamine, morpholine, piperazine, piperidine, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, diethanolamine, meglumine, ethylenediamine, N,N'-diphenylethylenediamine, N,N'-dibenzylethylenediamine, N-benzyl phenylethylamine, choline, choline hydroxide, dicyclohexylamine, metformin, benzylamine, phenylethylamine, dialkylamine, trialkylamine, thiamine, aminopyrimidine, aminopyridine, purine, spermidine; alkylphenylamine, glycinol, phenyl glycinol; glycine, alanine, valine, leucine, isoleucine, norleucine, tyrosine, cystine, cysteine, methionine, proline, hydroxy proline, histidine, ornithine, lysine, arginine, serine, threonine, phenylalanine; unnatural amino acids; D-isomers or substituted amino acids; guanidine, substituted guanidine wherein the substituents are selected from nitro, amino, alkyl, alkenyl, alkynyl, ammonium or substituted ammonium salts and aluminum salts; sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates,

citrates, succinates, palmoates, methanesulphonates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, or ketoglutarates.

The compounds of the present invention, may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. Therefore, where a compound is chiral, the separate enantiomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of the two enantiomers. Also included within the scope of the invention are polymorphs as well as hydrates of the compounds of the instant invention.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such pro drugs will be functional derivatives of the compounds of this invention which are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

The terms "individual," "subject," "host," and "patient" refer to any subject for whom diagnosis, treatment, or therapy is desired. In one embodiment, the individual, subject, host, or patient is a human. Other subjects may include, but are not limited to, animals including but not limited to, cattle, sheep, horses, dogs, cats, guinea pigs, rabbits, rats, primates, opossums and mice. Other subjects include species of bacteria, phages, cell cultures, viruses, plants and other eucaryotes, prokaryotes and unclassified organisms.

The terms "treatment," "treating," "treat," and the like are used herein to refer generally to obtaining a desired pharmacological and/or physiological effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete

stabilization or cure for a disease and/or adverse effect attributable to the disease. "Treatment" as used herein covers any treatment of a disease in a subject, particularly a human, and includes: (a) preventing the disease or symptom from occurring in a subject which may be predisposed to the disease or symptom, but has not yet been diagnosed as having it; (b) inhibiting the disease symptom, i.e., arresting its development; or (c) relieving the disease symptom, i.e., causing regression of the disease or symptom.

The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or patient that is being sought by a researcher.

The term "alkyl" shall mean straight, branched or monocyclic alkanes, alkenes or alkynes of the specified number of carbon atoms. Preferably, the term "alkyl-" refers to straight or branced chain alkanes of C_{1-10} carbon atoms, or any number within this range (i.e., methyl, ethyl, I-propyl, 2-propyl, n-butyl, s-butyl, t-butyl, etc.).

The term "aryl" as used herein, refer to a substituted or unsubstituted 5 or 6 membered monocyclicor bicyclic aromatic ring wherein the ring contains 0, 1, 2, 3 or 4 heteroatoms chosen from N, O or S. Examples of the preferred aryl systems include, but are not limited to, benzene, pyridine, pyrrole, furan, thiophene, triazine, triazoles, pyrazine, pyrimidine, pyridazine, naphthalene, pyridine, quinoline, benzofuran, dihydrobenzofuran, benzopyran, dihydrobenzopyran, indole, azaindole, pyrazole, benzothiazole, benzoxazole and the like.

The terms "polycyclic" or "polycyclyl," as used herein, refer to unsubstituted or substituted fused or bridged polycyclic systems containing from 7 to 20 carbon atoms and which can contain one or more degrees of unsaturation. Preferably, the term "polycyclyl" refers to unsubstituted or substituted fused or bridged bi- or tri-cyclic systems containing from 7-15 carbon atoms and which are saturated or can contain one or six degrees of unsaturation. More preferably, the term "polycyclyl" refers to unsubstituted or substituted fused or bridged bi- or tri-cyclic systems containing from 8-12 carbon atoms and which can contain upto six degrees of unsaturation. Examples of prefered polycyclyl systems include, but are not limited to, naphthalene, tetraline, dihydro naphthalene, decahydronaphthalene, quinoline, tetrahydro quinoline, iso quinoline, tetrahydro isoquinoline, quinazolinone, benzoxazine, dihydrobenzoxazine, benzothiazine, dihydrobenzothiazine, indole,

dihydro indole, isoindole, dihydro isoindole, pyrrolo oxazole, pyrrolizidine, benzotriazole, benzoxazole, benzothiazole, imidazopyridazine, pyrazolopyrimidine, pyrazolopyridine, benzimidazole, indazole, furopyridine, benzofuran, benzothiophene, pyrindine, pyrazolodiazepine, benzotriazene, azirinoindole, pyrazoloquinoline, imidazoquinoline, benzothiazene, phthalazene, quinazoline, quinoxaline, benzoxathiin, carbazole, naphthofuran, naphthopyrans, benzothiophene, acridine, benzoisoquinoline, benzoquinoline.

The term "halogen" shall include iodine, bromine, chlorine and fluorine.

The term "alkyl" shall mean straight, branched or monocyclic alkanes, alkenes or alkynes of the specified number of carbon atoms. Preferably, the term "alkyl-" refers to straight or branced chain alkanes of C_{1-10} carbon atoms, or any number within this range (i.e., methyl, ethyl, I-propyl, 2-propyl, n-butyl, s-butyl, t-butyl, etc.).

The term "hydroxyalkyl" is (C_1-C_{10})alkyl-OH, wherein (C_1-C_{10})alkyl group is as defined above. Exemplary hydroxyalkyl groups include but are not limited to hydroxy methyl, hydroxyethyl, hydroxypropyl, hydroxyisopropyl, hydroxybutyl, hydroxyisobutyl, hydroxyter. butyl and the like.

The term "alkoxy" is (C_1-C_{10})alkyl-O-, wherein (C_1-C_{10})alkyl group is as defined above. Exemplary alkoxy groups include but are not limited to methoxy, ethoxy, propyloxy, butyloxy, iso-propyloxy and the like.

The term "alkoxycarbonyl" is (C_1-C_{10})alkyl-O-CO-, wherein (C_1-C_{10})alkyl group is as defined above. Exemplary alkoxycarbonyl groups include but are not limited to methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl and the like.

The term "aryloxy" is aryl-O- wherein aryl group is as defined above. Exemplary aryloxycarbonyl groups include, but are not limited to, phenoxy, naphthyloxy and the like.

The term "aryloxycarbonyl" is aryl-O-CO-, wherein aryl group is as defined above. Exemplary aryloxycarbonyl groups include, but are not limited to, phenoxycarbonyl, naphthyloxycarbonyl and the like.

The term "arylalkoxy" is aryl-(C_1-C_{10})alkoxy, where aryl and (C_1-C_{10})alkoxy are as defined above. Exemplary arylalkoxy groups include, but are not limited to benzyloxy, phenethyloxy and the like.

The term "arylalkoxycarbonyl" is aryl-(C_1-C_{10})alkoxy-CO-, where aryl and (C_1-C_{10})alkoxy are as defined above. Exemplary aralkoxycarbonyl groups include, but are not limited to benzyloxycarbonyl, 2-phenethyloxycarbonyl and the like.

The term "alkylcarbonyloxy" is (C_1-C_{10})alkyl-CO-O, wherein (C_1-C_{10})alkyl group is as defined above. Exemplary alkylcarbonyloxy groups include, but are not limited to methylcarbonyloxy, ethylcarbonyloxy, propylcarbonyloxy and the like.

The term "alkoxycarbonylamino" is (C_1-C_{10})alkyl-O-CO-amino, wherein (C_1-C_{10})alkyl group is as defined above. Exemplary alkoxycarbonylamino groups include, bit are not limited to methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino and the like.

The term "aryloxycarbonylamino" is aryl-O-CO-amino, wherein aryl group is as defined above. Exemplary aryloxycarbonylamino groups include, but are not limited to, phenoxycarbonylamino, naphthyloxycarbonylamino and the like.

The term "arylalkoxycarbonylamino" is aryl-(C_1-C_{10})alkoxy-CO-amino, where aryl and (C_1-C_{10})alkoxy are as defined above. Exemplary arylalkoxycarbonylamino groups include, but are not limited to, benzyloxycarbonylamino, 2-phenethyloxycarbonylamino and the like.

The term "alkylthio" is (C_1-C_{10})alkyl-S-, where (C_1-C_{10})alkyl is as defined above. Exemplary alkylthio groups include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, t-butylthio and the like.

The term "thioalkyl" is –S-(C_1-C_{10})alkyl where (C_1-C_{10})alkyl is as defined above. Exemplary thioalkyl groups include, but are not limited to, thiomethyl, thioethyl, thiopropyl, thioisopropyl, thiobutyl, thioisobutyl, thiot butyl and the like

The term "arylalkyl" is aryl(C_1-C_{10})alkyl where aryl and (C_1-C_{10})alkyl groups are as defined above. Exemplary arylalkyl groups include, but are not limited to, benzyl, phenethyl, naphthylmethyl, naphthylethyl and the like.

The term "arylaminocarbonyl" is aryl-amino-CO- where aryl is as defined above. Exemplary arylaminocarbonyl group include, but are not limited to, benzylaminocarbonyl, naphthylaminocarbonyl and the like.

The term "aminoalkyl" is amino(C_1-C_{10})alkyl where (C_1-C_{10})alkyl group is as defined above. Exemplary aminoalkyl group include, but are not limited to

aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminoisobutyl, aminot-butyl and the like.

The term "acylamino" is H-CO-amino or (C_1-C_{10})alkyl-CO-amino, where (C_1-C_{10})alkyl group is as defined above. Exemplary acylamino groups include, but are not limited to, acetylamino, propanoylamino, butanoylamino, pentanoylamino, and the like.

The term "acylaminoalkyl" is H-CO-amino(C_1-C_{10})alkyl or (C_1-C_{10})alkyl-CO-amino(C_1-C_{10})alkyl where (C_1-C_{10})alkyl group is as defined above. Exemplary acylaminoalkyl groups include, but are not limited to acetylaminomethyl, acetylaminoethyl, acetylaminopropyl, propanoylaminomethyl, butanoylaminomethyl, pentanoylaminomethyl, and the like.

The term "alkoxyalkyl" is (C_1-C_{10})alkyl-O-(C_1-C_{10})alkyl where (C_1-C_{10})alkyl is as defined above. Exemplary alkoxyalkyl group includes, but are not limited to methoxymethyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, ethoxyisobutyl, and the like.

The term "aroyl" is aryl-CO- where aryl is as defined above. Exemplary aroyl group include, but not limited to benzoyl, 1-naphthoyl and the like.

The term "cycloalkyl" is (C_3-C_8)cycloalkyl group. Exemplary cycloalkyl groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "heterocyclyl" is a non-aromatic saturated monocyclic or multicyclic ring system of about 5 to about 10 carbon atoms, having at least one hetero atom selected from O, S or N. Exemplary heterocyclyl groups include, but are not limited to aziridinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl and the like.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs. Although any methods, devices, and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods, devices and materials are now described.

All publications and patents mentioned herein are incorporated herein by reference for the purpose of describing and disclosing, for example, the constructs and methodologies that are described in the publications, which might be used in connection with the presently described invention. The publications discussed above and throughout the text are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention.

It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, constructs, and reagents described herein and as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

The dosage regimen utilizing. the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician, veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via

transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or betalactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, soaium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polYmers as targetable drug carriers. Such polymers can include

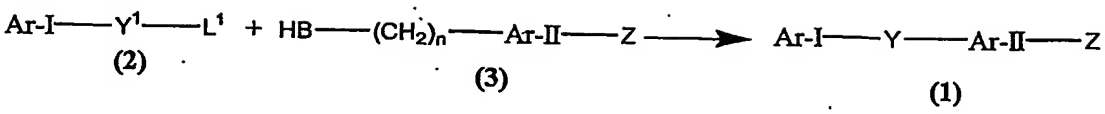
polYVinylpyrrolidone, pyran copolYmer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polYmers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolYmers of polyactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolYmers of hydrogels.

The compounds of formula 1 can generally be prepared, for example in the course of a convergent synthesis, by linkage of two or more fragments which can be derived retrosynthetically from the formula 1. in the preparation of compounds of formul 1, it may be generally necessary in the course of synthesis temporarily block functional groups which could lead to undesired reactions or side reactions in a synthetic step by protective group suited to the synthesis problem and known to the person skilled in the art. The method of fragment coupling is not restricted to the following examples, but is generally applicable for synthesis of compounds of formula 1.

The novel compounds of the present invention were prepared according to the procedure of the following schemes and examples, using appropriate materials and are further exemplified by the following specific examples. The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted.

The following Schemes and Examples describe procedures for making representative compounds of the present invention. Moreover, by utilizing the procedures described in detail, one of ordinary skill in the art can readily prepare additional compounds of the present invention claimed herein.

Route 1:

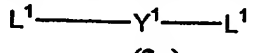


(2) (3) (1)

reaction of compound of formula (2) where Y^1 represents $(CH_2)_m$, $(CH_2)_lB(CH_2)_n$, L^1 represents a leaving group selected from halogen or mesyloxy and Ar-I is as defined, with a compound of formula (3) wherein the all the symbols are as defined to produce a compound of the formula (1) wherein Y represents $(CH_2)_mB(CH_2)_n$, $(CH_2)_l$ $B(CH_2)_mB(CH_2)_n$ and all other symbols are as defined above may be carried out in the presence of a solvent such as diethyl ether, THF, DMF, DMSO, DME, toluene, benzene, acetone, acetonitrile and the like or a mixture thereof. The reaction may be carried out in an inert atmosphere, which may be maintained by using inert gases such as N_2, Ar, He and the like. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3 or NaH or mixtures thereof. The reaction temperature may range from -20 °C – 120 °C, preferably at a temperature in the range of 0 °C – 120 °C. The duration of the reaction may range from 1 to 48 hours. Phase transfer catalyst such as tetraalkylammonium halides or hydroxides or bisulphates may be employed.

Alternatively, when L^1 = OH and B = Oxygen, Mitsunobu reaction conditions may be employed to obtain compound of formula (1)

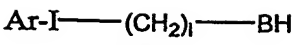
The intermediate (2) may be obtained by reacting Ar-I which as defined, with (2a)



(2a)

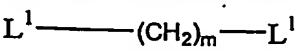
where Y^1 represents $(CH_2)_m$, $(CH_2)_lB(CH_2)_n$, L^1 represents a leaving group selected from halogen or mesyloxy in the presence of a solvent such as diethyl ether, THF, DMF, DMSO, DME, toluene, benzene, acetone, acetonitrile and the like or a mixture thereof and a base such as KOH, K_2CO_3, Na_2CO_3 or NaH. The reaction may be carried out in an inert atmosphere, which may be maintained by using inert gases such as N_2, Ar, He and the like.

Alternatively, the intermediate (2) where Y^1 is $(CH_2)_lB(CH_2)_m$ and L^1 represents a leaving group selected from halogen or mesyloxy may be obtained by reacting the compound of formula (2b)



(2b)

wherein Ar-I and B have the meaning as described, with (2c)



(2c)

where L^1 represents a leaving group selected from halogen or mesyloxy in the presence of a solvent such as diethyl ether, THF, DMF, DMSO, DME, toluene, benzene, acetone, acetonitrile and the like or a mixture thereof and a base such as K_2CO_3, Na_2CO_3 or NaH . The reaction may be carried out in an inert atmosphere, which may be maintained by using inert gases such as N_2, Ar, He and the like. The reaction temperature may range from -20 °C – 120 °C, preferably at a temperature in the range of 0 °C – 120 °C. The duration of the reaction may range from 1 to 48 hours. Phase transfer catalyst such as tetraalkylammonium halides or hydroxides or bisulphates may be employed.

Route 2:

(4) (5) (1)

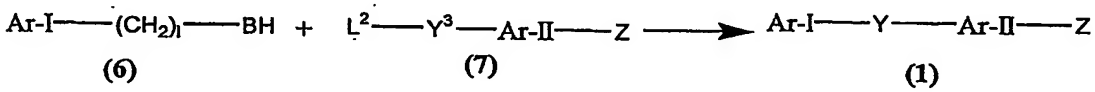
reaction of compound of formula (4) where Y^2 represents $(CH_2)_{m-1}$, $(CH_2)_mB(CH_2)_n$ and Ar-I is as defined with a compound of formula (5) where Ar-II and Z have the meaning as described, to produce a compound of the formula (1) wherein Y represents $(CH_2)_mB(CH_2)_n$, $B(CH_2)_mD(CH_2)_n$ and all other symbols are as defined above, may be carried out in two steps; the first step being the imine formation, followed by reduction. Formation of imine may be carried out in solvents such as benzene, toluene, chloroform, dichloromethane, MeOH, EtOH, *i*-PrOH and the like. The reaction may be effected in the presence of a catalyst such as pTsOH, NaOAc, BF_3.OEt, KOAc and the like or the mixtures thereof. The temperature of reaction may range from room temperature to the reflux temperature of the solvent used. The reaction time may be 2 h to 24 h, preferably in the range 2 h to 12 h.

The imine can also be obtained by the reaction of a compound of general formula (4) with a compound of formula (5) using solvent such as CH_2Cl_2, $CHCl_3$, chlorobenzene, benzene, THF, in the presence of catalyst such as p-toluenesulfonic acid, methanesulfonic acid, TFA, TfOH, BF_3-OEt_2 and the like. The reaction may also

be carried out in presence of activated molecular sieves. The temperature of the reaction may range from 10 °C to 100 °C, preferably at a temperature in the range from 10 °C to 60 °C. The reaction time may range from 1 h to 48 h.

The imine product thus obtained above may be reduced by using $Na(CN)BH_3$-HCl (ref: Hutchins, R. O. et al. *J. Org. Chem.* **1983**, *48*, 3433), $NaBH_4$, H_2-Pd]/C, H_2-Pt/C, H_2-Rh/C and the like in solvents such as methanol, ethanol and the like.

Route 3:

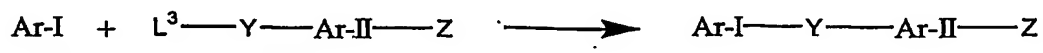


(6) (7) (1)

reaction of compound of formula (6) wherein all symbols are as defined with a compound of formula (7) Y^3 represents $(CH_2)_m$, $(CH_2)_mB(CH_2)_n$, L^2 represents a leaving group selected from halogen or mesyloxy, Ar-II and Z have the meaning as described to produce a compound of the formula (1) wherein Y represents $(CH_2)_mB(CH_2)_n$, $(CH_2)_lB(CH_2)_mB(CH_2)_n$ and all other symbols are as defined above, may be carried out in the presence of aprotic solvents such as diethyl ether, THF, DMF, DMSO, DME, toluene, benzene, acetone, acetonitrile and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere, which may be maintained by using inert gases such as N_2, Ar, He and the like. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3 or NaH or mixtures thereof. The reaction temperature may range from -20 °C – 120 °C, preferably at a temperature in the range of 0 °C – 120 °C. The duration of the reaction may range from 1 to 48 hours. Phase transfer catalyst such as tetraalkylammonium halides or hydroxides or bisulphates may be employed.

Alternatively, when L^2 = OH and B = Oxygen, Mitsunobu reaction conditions may be employed to obtain compound of formula (1)

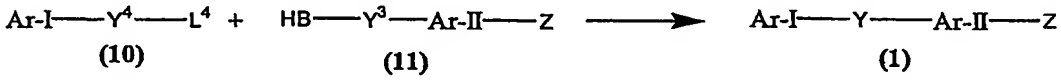
Route 4:



(8) (9) (1)

reaction of compound of formula (8) wherein Ar-I has the meaning as described with a compound of formula (9) where Y represents $(CH_2)_m$, $(CH_2)_mB(CH_2)_n$, $(CH_2)_lB(CH_2)_mB(CH_2)_n$, L^3 represents a leaving group selected from halogen or mesyloxy, Ar-II and Z have the meaning as described to produce a compound of the formula (1) wherein Y represents $(CH_2)_m$, $(CH_2)_mB(CH_2)_n$, $(CH_2)_lB(CH_2)_mB(CH_2)_n$, and all other symbols are as defined above, may be carried out in the presence of aprotic solvents such as diethyl ether, THF, DMF, DMSO, DME, toluene, benzene, acetone, acetonitrile and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere, which may be maintained by using inert gases such as N_2, Ar, He and the like. The reaction may be effected in the presence of a base such as KOH, K_2CO_3, Na_2CO_3 or NaH or mixtures thereof. The reaction temperature may range from -20 °C – 120 °C, preferably at a temperature in the range of 0 °C – 120 °C. The duration of the reaction may range from 1 to 48 hours. Phase transfer catalyst such as tetraalkylammonium halides or hydroxides or bisulphates may be employed.

Route 5:

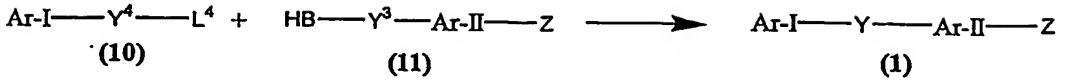


(10) (11) (1)

reaction of compound of formula (10) where Y^4 represents $(CH_2)_m$, $(CH_2)_mB(CH_2)_n$, L^4 represents a leaving group selected from halogen or mesyloxy, Ar-I has the meaning described, with a compound of formula (11) where Y^3 represents $(CH_2)_m$ and all other symbols are as described to produce a compound of the formula (1) wherein Y represents $(CH_2)_mB(CH_2)_n$ and all other symbols are as defined above, may be carried out in an inert atmosphere, which may be maintained by using inert gases such as N_2, Ar, He and the like. The reaction may be effected in the presence of a base such as NaH and a solvent such as DMF, THF, dioxane, ether or a mixture thereof. The reaction temperature may range from -20 °C – 120 °C, preferably at a temperature in the range of 0 °C – 120 °C. The duration of the reaction may range from 1 to 48 hours. Phase transfer catalyst such as tetraalkylammonium halides or hydroxides or bisulphates may be employed.

Alternatively, when L^4 = OH and B = Oxygen, Mitsunobu reaction conditions may be employed to obtain compound of formula (1)

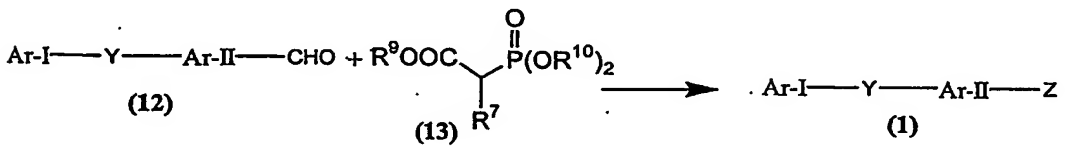
Route 6:



(10) (11) (1)

reaction of compound of formula (10) where Y^4 represents $(CH_2)_m$, $(CH_2)_mB(CH_2)_n$, L^4 represents a leaving group selected from halogen or mesyloxy, Ar-I has the meaning described, with a compound of formula (11) where B represents oxygen, Y^3 represents $(CH_2)_m$, Z represents $(CH_2)oACR^7R^8(CH_2)_pW$, o is 1, p is 0, A represents a bond, W represents CO_2R^9, R^7 and R^9 represent hydrogen and R^8 forms a bond with Ar-II and represents $(CH_2)_q$ where q represents 1 or 2, to produce a compound of the formula (1) wherein Y represents $(CH_2)_mB(CH_2)_n$ Z represents $(CH_2)oACR^7R^8(CH_2)_pW$, o is 1, p is 0, A represents a bond, W represents CO_2R^9, R^7 and R^9 represent hydrogen and R^8 forms a bond with Ar-II and represents $(CH_2)_q$ where q represents 1 or 2. and all other symbols are as defined above, may be carried out in an inert atmosphere, which may be maintained by using inert gases such as N_2, Ar, He and the like. The reaction may be effected in the presence of a base such as NaH and a solvent such as DMF, THF, dioxane, ether or a mixture thereof. The reaction temperature may range from -20 °C – 120 °C, preferably at a temperature in the range of 0 °C – 120 °C. The duration of the reaction may range from 1 to 48 hours. Phase transfer catalyst such as tetraalkylammonium halides or hydroxides or bisulphates may be employed.

Route 7:



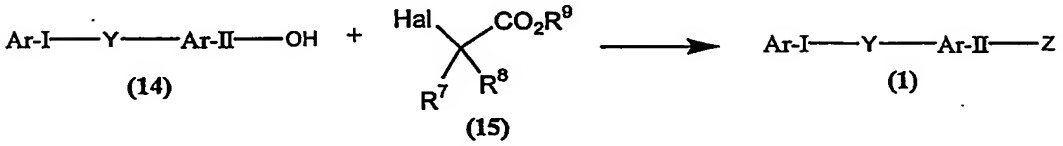
(12) (13) (1)

reaction of compound of formula (12) where all symbols have the meaning described with modified Wittig reagent (13) where R^9 represents substituted or unsubstituted groups selected from (C_{1-12})alkyl, cycloalkyl, aryl or aralkyl, R^7 represents (C_{1-12})alkoxy, R^{10} represents (C_{1-6})alkyl to produce a compound of formula (1) where Z represents $(CH_2)_oACR^7R^8(CH_2)_pW$ wherein A and R^8 together represent a bond, R^7 represents (C_{1-12})alkoxy, o and p is 0, W is CO_2R^9 and R^9 represents substituted or unsubstituted groups selected from (C_{1-12})alkyl, cycloalkyl, aryl or aralkyl and all

other symbols are as defined above may be carried out in the presence of a base such as alkali metal hydrides like NaH or KH; organolithiums such as CH_3Li, BuLi, LDA, TMEDA and the like; alkoxides such as NaOMe, NaOEt, K^+BuO^- and the like or mixtures thereof. The reaction may be carried out in the presence of solvents such as diethyl ether, THF, dioxane, DMF, DMSO, DME, toluene, benzene and the like or mixtures thereof. HMPA may be used as cosolvent. The reaction temperature may range from -78 ° to 50 °C, preferably at a temperature in the range of -10 °C to 30 °C. The reaction is more effective under anhydrous conditions.

Alternatively, the compound of formula (1) may be prepared by reacting the compound of formula (12) where all symbols are as defined earlier with Wittig reagents such as $HalPh_3P^+CH\text{-}(R^7)CO_2R^9$ under similar reaction conditions as described above.

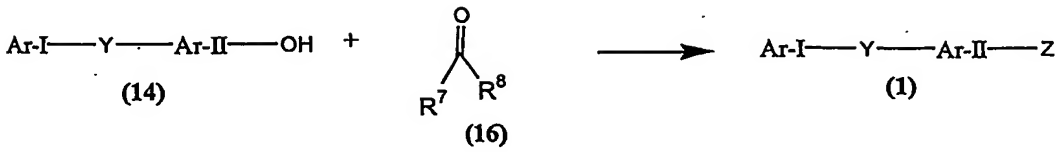
Route 8:



reaction of compound of formula (14) where all symbols have the meaning described with compound of formula (15) where R^7, R^8 and R^9 may be same or different and represent hydrogen, $C_{1\text{-}10}$alkyl or $C_{1\text{-}10}$alkoxy to produce a compound of formula (1) where Z represents $(CH_2)_oACR^7R^8(CH_2)_pW$ wherein A represent a bond, R^7 and R^8 represents $(C_{1\text{-}12})$alkyl, o and p is 0, W is CO_2R^9 and R^9 represents substituted or unsubstituted $(C_{1\text{-}12})$alkyl, may be carried out in the presence of an aprotic solvent such as THF, DMF, DMSO, DME, toluene, benzene, xylene and the like or mixtures thereof. The reaction may be carried out in the presence of an organic base such as triethylamine, collidine, lutidine and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere that may be maintained by using an inert gas such as nitrogen, helium or argon. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3, $NaNH_2$, n-BuLi, NaH, KH and the like. The reaction temperature may range from 0 to 120 °C, preferably in the range of 25 to 100 °C. The duration of the reaction may range from 1 to 72 h, preferably from 2 to 24 h.

Alternatively, Mitsunobu reaction conditions may be employed to obtain compound of formula (1)

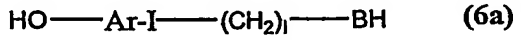
Route 9:



reaction of compound of formula (14) where all symbols have the meaning described with compound of formula (16) where R^7 and R^8 may be same or different and represent hydrogen, C_{1-10}alkyl or C_{1-10}alkoxy to produce a compound of formula (1) where Z represents $(CH_2)_oACR^7R^8(CH_2)_pW$ wherein A represent a bond, R^7 and R^8 represents (C_{1-12})alkyl, o and p is 0, W is CO_2R^9 and R^9 represents substituted or unsubstituted (C_{1-12})alkyl, may be carried out in the presence of chloroform-NaOH or chloroform-KOH and a solvent such as THF, dioxane, ethylether and the like or a mixture thereof at a temperature range – 25 °C to room temperature preferably O° C to room temperature.

Route 10: The compound of formula (1) where R^5 represent alkyl, alkenyl, $-S(O)_2-R^{10}$ or $-C(O)R^{10}$ where R^{10} is alkyl, alkoxy is obtained by reacting a compound of formula (I) where Y represents $(CH_2)_mNR^5(CH_2)_n$ and R^5 represents hydrogen, by reacting with RSO_2Cl, RC(O)Cl or an acid anhydride in the presence of a base selected from trialkylamine, pyridine or K_2CO_3 and solvent such as chloroform, dichloromethane or THF at a temperature range of -25 ° C to room temperature, preferably 0 °C to room temperature. Catalytic amounts of DMAP may also be used to accelerate the reaction.

Route 11: The intermediate (6) used in route 3 wherein Ar-I is substituted by mesyloxy may be obtained by mesylating the corresponding hydroxy substituted intermediate (6a)

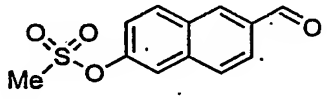


(6a)

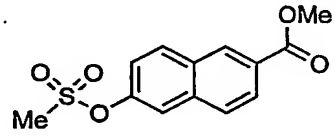
with mesyl chloride in the presence of a base such as trialkylamine, pyridine or K_2CO_3 and solvent such as chloroform, dichloromethane or THF at a temperature range of -25 ° C to room temperature, preferably 0 °C to room temperature.

The invention is explained in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

Preparation 1
6-methanesulfonyloxynapthyl-2-carboxaldehyde



Step 1: Methyl- 6-methanesulfonyloxy β- napthoate

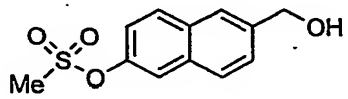


To a mixture of methyl 6-hydroxy β-napthoate (5.0 gm, 1.0 eq, 24.75 mmol) and Et_3N (8.6 mL, 2.5 eq, 61.88 mmol) in dry DCM (125 mL) stirred at 0 °C, methanesulfonylchloride (2.89 mL, 1.5 eq, 37.12 mmol) was added and stirring was continued for 5 hr. The reaction mixture was diluted with 200 mL of DCM and washed with aqueous citric acid followed by water and brine. Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as white solid (6 gm, 86 % yield). Mp: 106-108°C

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.23 (s, 3H); 3.99 (s, 3H); 7.47 (dd, J= 9.4, 2.4 Hz, 1H); 7.81 (d, J= 2.4 Hz, 1H); 7.89 (d, J=8.8 Hz, 3H); 8.02 (d, J=8.8 Hz, 1H); 8.13 (dd, J=8.8Hz, 1.4 Hz, 1H); 8.63 (s, 1H).

Mass m/z (ES): 281.1[M+1], 298.1 [$M+NH_4^+$], 303.0 [M+Na], 578.3 [$M_2+NH_4^+$], 583.3 [M_2+Na].

Step 2: **6-(Methanesulfonyloxy) napth-2-ylmethyl alcohol**



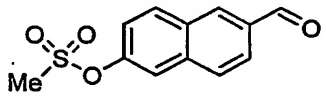
A solution of methyl- 6-methanesulfonyloxy β- napthoate (6 gm, 1 eq, 21.4 mmol) obtained in step1 of preparation 1, in dry THF (107 mL) was cooled up to -70 °C, and then DIBAL (53 mL, 3 eq, 64.2 mmol) was added drop wise with constant stirring at -70 °C. After the addition, the reaction mixture was slowly allowed to attain RT (4 hr). Reaction mixture was quenched with Methanol (150 mL), followed by the addition of saturated solution of Na_2SO_4. Finally reaction mixture was filtered through celite. Filterate was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as white solid (2.9 gm, 53 % yield). Mp: 96-98 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.19 (s, 3H); 4.87(s, 2H); 7.40(dd, J= 9.2, 2.4 Hz, 1H); 7.54 (d, J= 8.8 Hz, 1H); 7.75(d, J=2 Hz, 1H); 7.81-7.89 (aromatics, 3H)

IR (neat) cm^{-1}:

Mass m/z (ES): 270.3 [$M+NH_4^+$], 275.3 [M+Na], 522.5 [$M_2+NH_4^+$].

Step 3: **6-(Methanesulfonyloxy) napthyl-2-carboxaldehyde**



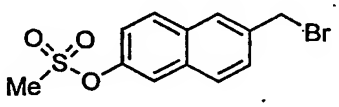
To a stirred solution of 6-methanesulfonyloxynapth-2-ylmethyl alcohol (2.9 gm, 1 eq, 11.51 mmol) obtained in step 2 of preparation 1 and activated molecular sieves (4A) in dry DCM (60 mL), pyridiniumdichromate (4.75 gm, 1.1 eq, 12.65 mmol) was added at 0 °C. After the addition, the reaction mixture was allowed to stir at RT for 15 hr. Reaction mixture was filtered through celite, filtrate was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as white solid (1.2 gm, 41% yield). Mp: 90-92 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.25 (s, 3H); 7.52 (dd, J= 8.8, 2.5 Hz, 1H); 7.83 (d, J= 2 Hz, 1H); 7.92-8.10 (aromatics, 3H); 8.37 (s, 1H); 10.17 (s, 1H).

IR (neat) cm^{-1}: 2932, 1681, 1624, and 1469.

Mass m/z(CI): 251 [M + 1].

Preparation 2
6-(Methanesulfonyloxy) napth-2-ylmethyl bromide



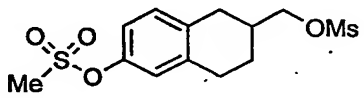
A mixture of 6-methanesulfonyloxynapth-2-ylmethanol (2 gm, 1eq, 7.9 mmol) obtained in step 2 of preparation 1, CBr_4 (2.88 gm, 1:1 eq, 8.69 mmol) and PPh_3 (3.10 gm, 1.5 eq, 11.85 mmol) in dry THF (40 mL) was stirred at RT for 17 h. Reaction mixture was condensed and diluted with ethyl acetate (100 mL) and washed with water. Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as white solid (770 mg, 31 % yield). Mpt: 100-102 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.19 (s, 3H); 4.65 (s, 2H); 7.42 (dd, J= 9, 2.4 Hz, 1H); 7.57 (dd, J= 8.4, 1.4 Hz, 1H); 7.75 (d, J= 2.2 Hz, 1H); 7.82-7.90 (aromatics, 3H)

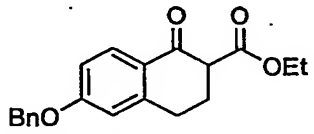
IR (neat) cm^{-1}: 2925, 1360, and 1173.

Mass m/z(CI): 315 [M (^{79}Br)+ 1], 317 [M (^{81}Br)+1]

Preparation 3
1, 2,3,4-Tetrahydro-6-(methanesulfonyloxy)-napth-2-ylmethyl methanesulfonate



Step 1: **Ethyl-6-benzyloxy-1, 2,3,4-tetrahydro-1-oxo-β-napthoate**



To a suspension of NaH (816 mg, 60 % in oil, 2 eq, 20.42 mmol) in 40 mL dry THF, diethylcarbonate (3.7 mL, 3 eq, 30.64 mmol) was added, and the mixture was heated at 60 °C. To that a solution of 6-(benzyloxy)tetralone (2.57 g, 1 eq, 10.21 mmol) in 10 mL THF was added and the heating was continued for another

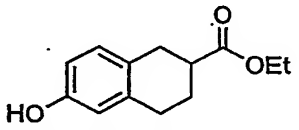
4 hours. Reaction mixture was condensed and diluted with ethyl acetate (100 mL) and washed with water. Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick liquid (2.58 g, 78 % yield). TLC as well as ^{1}H-NMR indicates that the compound is a mixture keto/enol tautomers of 70:30 ratio. For clarification, ^{1}H-NMR data is given here for the keto form.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28 (t, J=7 Hz, 3H); 2.30-3.10 (m, 4H); 3.54 (dd, J= 10, 4.5 Hz, 1H); 4.23 (q, J= 7 Hz, 2H); 5.11 (s, 2H); 6.77-6.92 (aromatics, 2H); 7.32-7.44 (aromatics, 5 H); 8.02 (d, J= 8.6 Hz, 1H).

IR (neat) cm^{-1}: 2936, 1737, 1677, and 1600.

Mass m/z(CI): 325 [M+1].

Step 2: **Ethyl-6-hydroxy-1, 2,3,4-tetrahydro-β-napthoate**



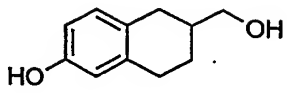
Ethyl-6-benzyloxy-1, 2,3,4-tetrahydro-1-oxo-β-napthoate (460 mg, 1.42 mmol) was hydrogenated under H_2 (5 psi pressure) at RT for 6-7 h using 10%-Pd/C (285 mg) as catalyst in a combination of solvents EtOH (14 mL) / water (1.4 mL) / conc. HCl (365 μL) to obtain the desired compound as white solid (250 mg, 80 % yield) after usual workup and purification through column chromatography (ethyl acetate/hexane). Mp: 80-82 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28 (t, J=7.2 Hz, 3H); 1.78-1.85 (m, 1H); 2.15-2.22 (m, 1H); 2.65-2.72 (m, 1H); 2.78-2.82 (m, 2H); 2.85-2.95 (m, 2H); 4.17 (q, J= 7.2 Hz, 2H); 4.64 (s, 2H); 6.55-6.62 (aromatics, 2H); 6.95 (d, J= 8 Hz, 1H).

IR (neat) cm^{-1}: 3397, 2934, 1737, 1707, and 1611.

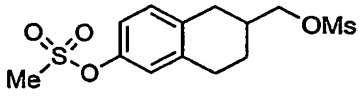
Mass m/z(CI): 3221 [M+1].

Step 3: **6-Hydroxy-1, 2,3,4-tetarhydronapth-2-ylmethyl alcohol**



A solution of ethyl-6-hydroxy-1, 2,3,4-tetrahydro-β-napthoate (480 mg, 1 eq, 2.184 mmol) obtained in step 1 of preparation 3, in dry THF (22 mL) was cooled up to -70 °C, and then DIBAL (10.8 mL, 6eq, 13.1mmol) was added drop wise with constant stirring at -70 °C. After the addition, the reaction mixture was slowly allowed to attain RT (4 hr). Reaction mixture was quenched with methanol (40mL), followed by the addition of saturated solution of Na_2SO_4. Finally reaction mixture was filtered through celite. Filtrate was dried (Na_2SO_4), condensed, and the residue, as a crude, was directly used for next reaction.

Step 4: **1, 2,3,4-Tetrahydro-6- (methanesulfonyloxy)-napth-2-ylmethyl methanesulfonate**



To a stirred solution of 6-Hydroxy-1,2,3,4-tetarhydronapth-2-ylmethyl alcohol (280 mg, 1 eq, 1.36 mmol) obtained in step2 of preparation 3, and Et_3N (1.3 mL, 6 eq, 8.15 mmol) in dry DCM (7 mL) at 0 °C, methanesulfonylchloride (0.316 mL, 3 eq, 4.07 mmol) was added and stirring was continued for 5 h. The reaction mixture was diluted with 50 mL of DCM and washed with citric acid solution followed by water and brine. Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (430 mg, 95 % yield).

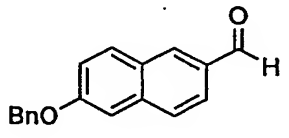
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.45-1.55 (m, 1H); 1.2.00-2.06 (m, 1H); 2.20-2.30 (m, 1H); 2.56 (dd, J= 16, 10 Hz, 1H); 2.84-3.03 (m 3H); 3.04 (s, 3H); 3.13 (s, 3H); 4.18-4.25 (m, 2H); 7.00-7.05 (aromatics, 2H); 7.10-7.13 (aromatics, 1H).

IR (neat) cm^{-1}: 2937, 1352, 1173.

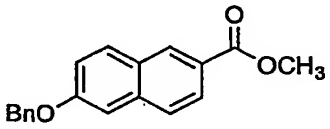
Mass m/z (CI): 335 [M + 1]

Preparation 4

6-benzyloxynapthyl-2-carboxaldehyde



Step: 1 **Methyl-6-benzyloxy-β-napthoate**



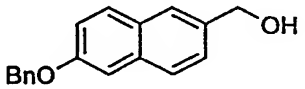
A mixture of Methyl-6-hydroxy-β-napthoate (6 g, 1 eq, 29.70 mmol), benzyl bromide (3.9 mL), and anhydrous K_2CO_3 (8.2 g, 2 eq, 59.41 mmol) in dry DMF was stirred at RT for 16 hr. Reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (3x100 mL). Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as white solid (8.4 g, 98 % yield). Mp: 149-151 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.97 (s, 3H); 5.21(s, 2H); 7.30-7.48 (aromatics, 7H); 7.75 (d, J= 8.6 Hz, 1H); 7.87 (d, J= 8.6 Hz, 1H); 8.03 (d, J= 8.6 Hz, 1H); 8.54 (s, 1H).

IR (neat) cm^{-1}: 3437, 2924, 1716, and 1624.

Mass m/z (CI): 293 [M + 1].

Step: 2 **6-benzyloxynapth-2-ylmethyl alcohol**



A solution of Methyl-6-benzyloxy-β-napthoate (8 g, 1 eq, 27.39 mmol) obtained) in step1 of preparation 4, in dry THF (200 mL) was cooled up to -70 °C, and then DIBAL (68 mL, 3 eq, 82.19 mmol) was added drop wise with constant stirring at -70 °C. After the addition, the reaction mixture was slowly allowed to attain RT (5 h). Reaction mixture was quenched with Methanol (250 mL), followed by the

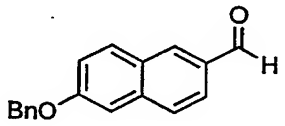
addition of saturated solution of Na_2SO_4. Finally reaction mixture was filtered through celite. Filtrate was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as white solid (7.1 g, 98 % yield). Mp: 130-132 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.71 (t, J=5.8 Hz, OH); 4.82 (d, J=5.8 Hz, 2H); 5.18(s, 2H); 7.24 (d, J=7.4 Hz, 2H); 7.34-7.51(aromatics, 6H); 7.71-7.77 (aromatics, 3H)

IR (neat) cm^{-1}: 2924, 1694, and 1617.

Mass m/z (CI): 265 [M + 1], 264 [M], 247 [M-OH].

Step: 3 **6-benzyloxynapthyl-2-carboxaldehyde**



To a solution of 6-benzyloxynapth-2-ylmethyl alcohol (7.1 gm, 1eq, 27.12 mmol) obtained in step 2 of preparation 4 and activated molecular sieves (4 A) in dry DCM (135 mL), PDC (11.2 gm, 1.1 eq, 29.83 mmol) was added at 0 °C. After the addition, the reaction mixture was allowed to stir at RT for 15 hr. Reaction mixture was filtered through celite, filtrate was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as white solid (4.15 gm, 59 % yield). Mp: 102-104 °C.

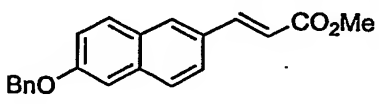
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 5.18 (s, 2H); 7.22-7.47 (aromatics, 7H); 7.73-7.90 (aromatics, 3H); 8.22 (s, 1H); 10.06 (s, 1H).

IR (neat) cm^{-1}: 2924, 1694, 1617.

Mass m/z (CI): 263 [M + 1].

Preparation 5

Methyl 3-(6-bezyloxynapth-2-yl) prop-2-enoate



To a stirred solution of 60 % NaH (915 mg, 1.5 eq, 22.90 mmol) in dry THF (60 mL) at 0 °C, trimethylphosphonoacetate (3.7 mL, 1.5 eq, 22.90 mmol) in dry THF (5 mL) was added drop wise. After the addition reaction mixture was stirred at RT for 1 h. Then again at 0 °C, 6-benzyloxynapthyl-2-carboxaldehyde (4.0 g, 1 eq, 15.27 mmol) obtained in step 3 of preparation 4, in dry THF (10 mL) was added drop wise and after the addition stirring was continued for 16 hr RT. Reaction mixture was concentrated to dryness, diluted with ethyl acetate (200 mL) and washed with water (2x150 mL). Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as white solid (4.6 g, 95 % yield). Mp: 132-134°C.

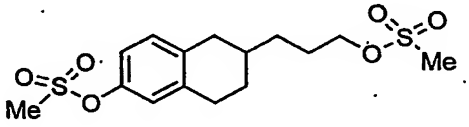
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.84 (s, 3H); 5.21 (s, 2H); 6.52 (d, J=16 Hz, 1H); 7.20-7.90 (aromatics, 11H).

IR (neat) cm^{-1}: 2925, 1718, and 1620.

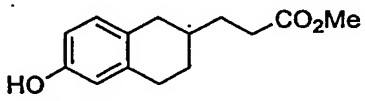
Mass m/z(CI): 319 [M + 1].

Preparation 6

1,2,3,4-terahydro-2- (3-Methanesulfonyloxypropyl)-6-(methanesulfonyloxy) naphthalene.



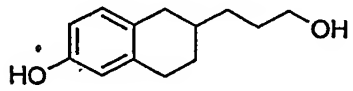
Step: 1 Methyl-3- (6-hydroxy-1, 2,3,4-tetrahydronapth-2-yl) propionate



A solution of Methyl 3-(6-bezyloxynapth-2-yl) prop-2-enoate (4.6 g, 1 eq, 14.46 mmol) obtained in preparation 5 and 10 % Pd-C (4.6 g) in ethyl acetate (250 mL) was kept in Parr hydrogenator at 60 psi H_2 pressure and at RT for 24 h. Reaction mixture was filtered through celite, dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (3.26 g, 90 % yield).

Mass m/z (ES): 252 [M + 18], 257 [M+23].

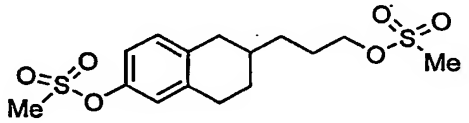
Step: 2 **3-(6-Hydroxy-1, 2;3,4-tetrahydronapth-2-yl) propan-1-ol**



A solution of Methyl-3- (6-hydroxy-1, 2,3,4-tetrahydronapth-2-yl) propionate (3.26 g, 1 eq, 14.17 mmol) obtained in step 1 of preparation 6, in dry THF (140 mL) was cooled up to -70 °C, and then DIBAL (35.1 mL, 3 eq, 42.52 mmol) was added drop wise with constant stirring at -70 °C. After the addition, the reaction mixture was slowly allowed to attain RT (5 h). Reaction mixture was quenched with Methanol (175 mL), followed by the addition of saturated solution of Na_2SO_4. Finally reaction mixture was filtered through celite. Filtrate was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (800 mg, 28 % yield).

Mass m/z (CI): 207 [M + 1].

Step: 3 **1,2,3,4-terahydro-2- (3-Methanesulfonyloxypropyl)-6-(methanesulfonyloxy) naphthalene**



To a stirred solution of 3-(6-Hydroxy-1, 2,3,4-tetrahydronapth-2-yl) propan-1-ol (720 mg, 1 eq, 1.36 mmol) obtained in step-2 of preparation 6, DMAP (catalytic amount) and Et_3N (3.9 mL, 6 eq, 28.41 mmol) in dry DCM (24 mL) at 0 °C, methanesulfonylchloride (1.10 mL, 3 eq, 14.21 mmol) was added and stirring was continued for 5 h. The reaction mixture was diluted with 50 mL of DCM and washed with citric acid solution followed by water and brine. Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (800 mg, 47 % yield).

^1H NMR ($CDCl_3$, 400 MHz) δ: 1.35-1.44 (m, 1H); 1.44-1.55 (m, 2H); 1.65-1.80 (m, 1H); 1.82-1.90 (m, 2H); 1.90-2.0 (m, 1H); 2.41 (dd, J=16.3, 10.6 Hz,

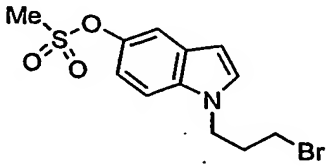
1H); 2.80-2.90 (m, 2H); 3.02 (s, 3H); 3.12 (s, 3H); 4.26 (t, J=6.8 Hz, 2H); 6.99-7.02 (aromatics, 2H); 7.02-7.10 (aromatics, 1H).

IR (neat) cm^{-1}: 2939, 1605, and 1496.

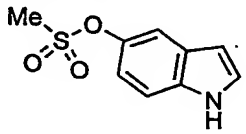
Mass m/z (CI): 363 [M + 1].

Preparation 7

3-(5-methanesulfonyloxyindol-1-yl) propyl bromide



Step1: **5-(Methanesulfonyloxy)indole**



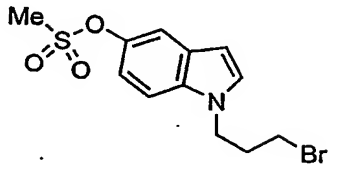
To a stirred solution of 5-hydroxyindole (5 g, 1 eq, 37.59 mmol), DMAP (catalytic amount) and Et_3N (10.5 mL, 2 eq, 75.19 mmol) in dry DCM (190 mL) at 0 °C, methanesulfonylchloride (2.92 mL, 1 eq, 37.59 mmol) was added and stirring was continued for 5 hr. The reaction mixture was diluted with 50 mL of DCM and washed with Citric acid solution followed by water and brine. Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as brown color solid (5.5 g, 69 % yield). Mp: 94-96 °C.

^1H NMR ($CDCl_3$, 200 MHz) δ: 3.11 (s, 3H); 6.55 (s, 1H); 7.09 (dd, J= 8.8 Hz, 2.4 Hz, 1H); 7.24-7.28 (aromatics, 1H); 7.36 (d, J=8.8 Hz, 1H); 7.54 (s, 1H); 8.31 (bs, NH).

IR (neat) cm^{-1}: 3397,2924, 1479, and 1365.

Mass m/z (CI): 212 [M+1].

Step: 2 **3-(5-methanesulfonyloxyindol-1-yl) propyl bromide**



A mixture of (5-Methanesulfonyloxy) indole (5.5 g, 1 eq, 23.69 mmol) obtained in step1 of preparation 7, and powdered KOH (1.99 g, 1.5 eq, 35.53 mmol) in dry DMSO (120 mL) was stirred at RT for 20 min. To that 1, 3-Dibromopropane (7.2 mL, 3 eq, 71.07 mmol) was added drop wise and the stirring was continued for 1h at RT. Reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (2x100 mL). Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (3.3 g, 42 % yield).

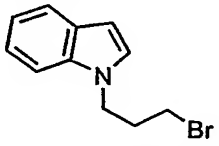
^1H NMR ($CDCl_3$, 200 MHz) δ: 2.31 (quintet, J=6.2 Hz, 2H); 3.10 (s, 3H); 3.26 (t, J= 6.2 Hz, 2H); 4.31 (t, J=6.2 Hz, 2H); 6.49 (d, J=2.4 Hz, 1H); 7.08-7.37 (aromatics, 3H); 7.50 (d, J=2.2 Hz, 1H).

IR (neat) cm^{-1}: 2932, 1481, and 1362.

Mass m/z (CI): 332 [M (^{79}Br)+ 1], 334 [M (^{81}Br)+ 1].

Preparation 8

3-(Indol-1-yl) propyl bromide



A mixture of indole (3 g, 1 eq, 25.63 mmol) and powdered KOH (2.18 g, 1.5 eq, 38.95 mmol) in dry DMSO (128 mL) was stirred at RT for 20 min. To that 1,3-dibromopropane (7.81 mL, 3 eq, 76.91 mmol) was added drop wise and stirring was continued for 1.5 h at RT. Reaction mixture was diluted with ethyl acetate (150 mL) and washed with water (2x100 mL). Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (2.1 g, 35 % yield).

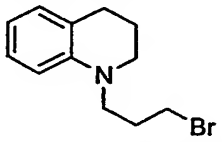
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.34 (quintet, J=6.2 Hz, 2H); 3.30 (t, J=6.2 Hz, 2H); 4.33 (t, J= 6.2 Hz, 2H); 6.5 (d, J=2.8 Hz, 1H); 7.07-7.25 (aromatics, 3H); 7.37 (d, J=8 Hz, 1H); 7.63 (d, J=8 Hz, 1H).

IR (neat) cm^{-1}: 2932, 1463, and 1314.

Mass m/z(CI): 238 [M (^{79}Br)+ 1], 240 [M (^{81}Br)+ 1].

Preparation 9

3-(1,2,3,4-terahydroquinolin-1-yl) propyl bromide



A mixture of 1, 2,3,4- tetrahydroquinoline (5 g, 1 eq, 37.59 mmol), 1,3-Dimromopropane (23 mL, 6 eq, 225.56 mmol) and anhydrous Na_2CO_3 (11.9 g, 3 eq, 112.77 mmol) in dry DMF (375 mL) was stirred at 70 °C for 4 hr. Reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (2x100 mL). Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (3.5 gm, 37 % yield).

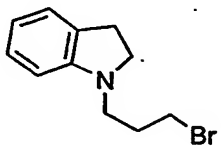
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.95 (quintet, J=6.2 Hz, 2H); 2.15(quintet, J=6.6 Hz, 2H); 2.75 (t, J= 6.2 Hz, 2H); 3.30 (t, J=5.5 Hz, 2H); 3.39-3.51 (m, 4H); 6.53-6.61(aromatics, 2H); 6.93-7.08 (m, 2H).

IR (neat) cm^{-1}: 3383(b), 2930,2842,1601,1503

Mass m/z (CI): 254 [M (^{79}Br)+ 1], 256 [M (^{81}Br)+ 1].

Preparation 10

3-(2,3-dihydroindol-1-yl) propyl bromide

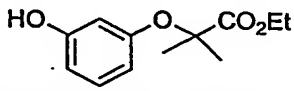


A mixture of indoline (3 g, 1 eq, 25.20 mmol), 1,3-di-bromopropane (15.4 mL, 6 eq, 151.26 mmol) and anhydrous Na_2CO_3 (8.0 g, 3 eq, 75.63 mmol) in dry DMF (250

mL) was stirred at 70 °C for 4 h. Reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (2x100 mL). Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (2.8 g, 47 % yield).

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.14 (quintet, J=6.2 Hz, 2H); 2.96 (t, J= 8.1 Hz, 2H); 3.23 (t, J= 6.4 Hz, 2H); 3.34 (t, J=8.1 Hz, 2H); 3.53 (t, J= 6.2 Hz, 2H); 6.51 (d, J=8.1 Hz, 1H); 6.65 (t, J=7.2 Hz, 1H); 7.03-7.09 (aromatics, 2H).
IR (neat) cm^{-1}: 2925, 1606, and 1489.
Mass m/z(CI): 240 [M (^{79}Br)+ 1], 242 [M (^{81}Br)+ 1].

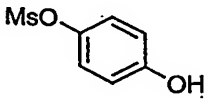
Preparation 11
Ethyl 2-methyl-2-(3-phenoxy)propanoate



The title compound was prepared following a literature procedure described in (Ref: JMC, 2001, 44, 2061).

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.25 (t, J= 7.1 Hz, 3H); 1.60 (s, 6H); 4.24 (q, J= 7.1 Hz, 2H); 5.35 (bs, 1H); 6.38-6.49 (aromatics 3H); 7.08 (t, J= 7.8 Hz, 1H)
IR (neat) cm^{-1}: 3418, 2989, 2940, 1732, 1595, 1486.
Mass m/z (CI): 225 [M+1].

Preparation 12
4-(Methanesulfonyloxy) phenol



To a stirred solution of Quinol (5 g, 1 eq, 45.45 mmol), Et_3N (12.7 mL, 2 eq, 90.9 mmol) and DMAP (1.1 g, 0.2 eq, 9.09 mmol) in dry THF (955 mL) at 0 °C, Mesyl chloride (2.6 mL, 0.75 eq, 34.09 mmol) was added drop wise. After the addition, stirring was continued at RT for 3 h. Reaction mixture was concentrated to dryness, diluted with ethyl acetate (400 mL) and washed with 10% citric acid solution (300

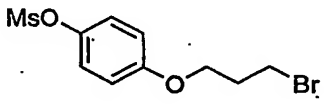
mL). Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as white solid (3 g, 35 % yield). Mp: 82-84 °C

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.13 (s, 3H); 5.44 (bs, 1H); 6.83 (t, J= 9.1 Hz, 1H); 7.15 (t, J= 9.1 Hz, 1H).

IR (neat) cm^{-1}: 3455, 2989, 2940, 1599, 1505.

Mass m/z (CI): 189 [M+1].

Preparation 13
3-(4-Methanesulfonyloxyphenoxy) propylbromide



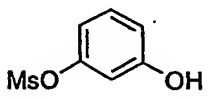
A mixture of 4-mesyloxy phenol (200 mg, 1 eq, 1.06 mmol) obtained in preparation 12, 1, 3- Dibromo propane (0.54 mL, 5 eq, 5.3 mmol) and powdered anhydrous K_2CO_3 (439 mg, 3 eq, 3.18 mmol) in acetone (22 mL) was stirred at 60 °C for 18 h. Reaction mixture was concentrated to dryness, diluted with ethyl acetate (100 mL) and washed with water (2x75 mL). Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (200 mg, 61 % yield).

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.32 (quintet, J= 6.1 Hz, 2H); 3.11 (s, 3H); 3.60 (t, J= 6.3 Hz, 2H); 4.10 (t, J= 5.8 Hz, 2H); 6.91 (t, J= 9.1 Hz, 1H); 7.21 (t, J= 9.1 Hz, 1H).

IR (neat) cm^{-1}: 3026, 2929, 1593, 1501.

Mass m/z (CI): 309 [M (^{79}Br) +1], 311 [M (^{81}Br) +1].

Preparation 14
3-(Methanesulfonyloxy) phenol



The title compound was prepared following the typical procedure described for **preparation 12.**

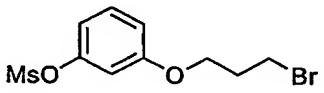
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.15 (s, 3H); 6.79-6.86 (aromatics, 3H); 7.26 (t, J= 9 Hz, 1H).

IR (neat) cm^{-1}: 3461, 3033, 2939, 1603, 1481.

Mass m/z (CI): 189 [M+1].

Preparation 15

3-(3-Methanesulfonyloxyphenoxy) propylbromide



The title compound was prepared following the typical procedure described for **preparation 13.**

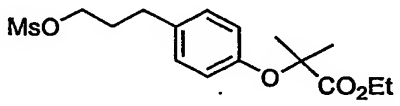
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.32 (quintet, J= 6.3 Hz, 2H); 3.14 (s, 3H); 3.60 (t, J= 6.3 Hz, 2H); 4.11 (t, J= 5.8 Hz, 2H); 6.80-6.90 (aromatics, 3H); 7.25-7.35 (aromatics, 1H).

IR (neat) cm^{-1}: 3028, 2938, 1607, 1586, 1485.

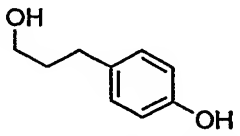
Mass m/z (CI): 309 [M(^{79}Br)+1], 311 [M(^{81}Br)+1].

Preparation 16

Ethyl 2-methyl-2-[4-{3-(methanesulfonyloxy) propyl} phenoxy] propanoate



Step: 1 **3-(4-hydroxyphenyl) propan-1-ol**



A suspension of LAH (10.5 g, w/w) in dry THF (500 mL) was refluxed for 3 hr. A solution of ethyl 3-(4-hydroxyphenyl) propionate (10 g, 1 eq, 55.55 mmol) in dry THF (50 mL) was added drop wise at reflux temperature. After the addition,

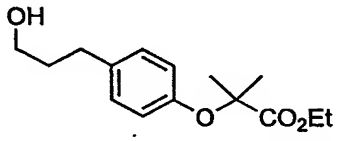
reaction mixture was refluxed for 6 hr. Reaction mixture was quenched with ethyl acetate (40mL, 4 eq with respect to LAH), followed by the addition of saturated Na_2SO_4 solution. To the workup mixture conc. HCl was added to adjust the pH at 7.0. Then reaction mixture was filtered through celite and washed with ethyl acetate. Combined filtrate was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as white solid (5.7 g, 68 % yield). Mp: 52-54°C.

^{1}H.NMR ($CDCl_3$, 200 MHz) δ: 1.78-1.86 (m, 2H); 2.63 (t, J=7.9 Hz, 2H); 3.67 (t, J= 6.3 Hz, 2H); 6.74(d, J= 8.8 Hz, 2H); 7.05(d, J= 8.8 Hz, 2H).

IR (neat) cm^{-1}: 3485, 3029, 2940, and 1505.

Mass m/z (CI): 152 [M+1].

Step: 2 **Ethyl 2-methyl-2- [4-(3-hydroxypropyl) phenoxy] propionate**



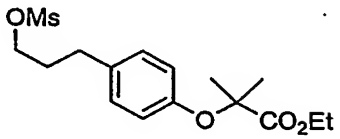
A mixture of 3-(4-hydroxyphenyl) propan-1-ol (3 g, 1 eq, 19.74 mmol), obtained in **step 1** of **preparation 16**, ethyl 2-bromoisobutyrate (8.69 mL, 3 eq, 59.21 mmol), and powdered anhydrous K_2CO_3 (13.6 g, 5 eq, 98.7 mmol) in EtOH (98 mL) was heated at 70 °C for 17 h. Reaction mixture was condensed to dryness, diluted with ethyl acetate (200 mL) and washed with water (2x100 mL). Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (4.7 g, 89 % yield).

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.25 (t, J= 7.2 Hz, 3H); 1.57 (s, 6H); 1.82-1.89 (m, 2H); 2.64(t, J= 7.2 Hz, 2H); 3.65(t, J= 6.4 Hz, 2H); 4.23 (q, J= 7.2 Hz, 2H); 6.77 (d, J= 8.8 Hz, 2H); 7.05 (d, J= 8.8 Hz, 2H)

IR (neat) cm^{-1}: 3406, 2939, 1733, and 1509.

Mass m/z (CI): 267 [M+1].

Step: 3 Ethyl 2-methyl-2-[4-(3-methanesulfonyloxypropyl)phenoxy]propionate



To a stirred solution of ethyl 2-methyl-2-[4-(3-hydroxypropyl)phenoxy] propionate (4.7 g, 1 eq, 17.66 mmol), obtained in **step 2 of preparation 16**, DMAP (catalytic amount) and Et_3N (4.9 mL, 2 eq, 35.34 mmol) in dry DCM (89 mL) at 0 °C, methanesulfonylchloride (1.37 mL, 1 eq, 17.66 mmol) was added and stirring was continued for 5 h. The reaction mixture was diluted with 50 mL of DCM and washed with citric acid solution followed by water and brine. Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (4 g, 66 % yield).

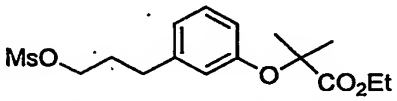
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (t, J= 7 Hz, 3H); 1.57 (s, 6H); 2.00-2.07 (m, 2H); 2.68 (t, J= 7.2 Hz, 2H); 2.97 (s, 3H); 4.19-4.26 (m, 4H); 6.78 (d, J= 8.8 Hz, 2H); 7.04 (d, J= 8.8 Hz, 2H)

IR (neat) cm^{-1}: 2939, 1733, and 1509.

Mass m/z (ES): 345 [M+1], 362[M+18], 367[M+23].

Preparation 17

Ethyl 2-methyl-2-[3-{3-(methanesulfonyloxy)propyl}phenoxy]propanoate



Prepared following the same procedure as described in the above preparation.

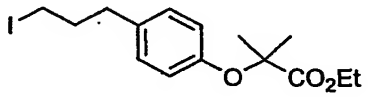
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.25 (t, J= 7.1 Hz, 3H); 1.59 (s, 6H); 2.00-2.11 (m, 2H); 2.69 (t, J= 7.5 Hz, 2H); 2.99 (s, 3H); 4.17-4.29 (m, 4H); 6.63-6.84 (aromatics 3H); 7.16 (t, J= 7.8 Hz, 1H)

IR (neat) cm^{-1}: 2940, 1732.

Mass m/z (CI): 345 [M+1].

Preparation 18

Ethyl 2-methyl-2- [4-(3-iodopropyl) phenoxy] propanoate

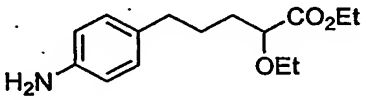


A mixture of Ethyl 2-methyl-2- [4-(3-methanesulfonyloxypropyl) phenoxy] propionate (500 mg, 1 eq, 1.45 mmol) obtained in **preparation 16**, and NaI (2.17 g, 10 eq, 14.5 mmol) in dry THF (8 mL) was stirred at 50 °C for 4 h. Reaction mixture was diluted with ethyl acetate (100 mL) and washed with water. Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (495 mg, 90 %).

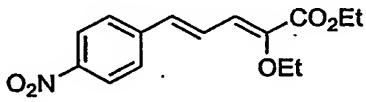
Mass m/z (CI): 377 (M+1).

Preparation 19

Ethyl-2-ethoxy-5- (4-aminophenyl) pentanoate

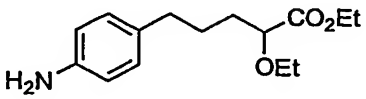


Step: 1 **Ethyl 2-ethoxy-5- (4-nitrophenyl) penta-2, 4-dienoate**



To a stirred solution of NaH (680 mg, 60 % in oil, 1.5 eq, 16.95 mmol) in dry THF (50 mL) at 0 °C, 2-ethoxy triethylphosphonoacetate (4.5 gm, 1.5 eq, 16.95 mmol) in dry THF (5 mL) was added drop wise. After the addition reaction mixture was stirred at RT for 2 h. Then again at 0 °C, 4-Nitrocinnamaldehyde (2.0 g, 1 eq, 11.29 mmol), was added in portion wise and after the addition was over, stirring was continued for 6 h at RT. Reaction mixture was wuenched with methanol, concentrated to dryness, diluted with ethyl acetate (200 mL) and washed with water (2x150 mL). Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as a thick mass as a mixture of 2,3- E and Z isomers (TLC), 2.6 g, 80 % yield). This was used for step 2 (next reaction).

Step: 2 **Ethyl-2-ethoxy-5- (4-aminophenyl) pentanoate**



A solution of Ethyl 2-ethoxy-5-(4-nitrophenyl)penta-2,4-dienoate (2 g, 1 eq, 6.87 mmol) obtained in **step 1 of preparation 19** and 10 % Pd/C (2 g) in ethyl acetate (150 mL) was hydrogenated at 60 psi H_2 pressure and at RT for 7 h. Reaction mixture was filtered through celite, dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (1.72 g, 94 % yield).

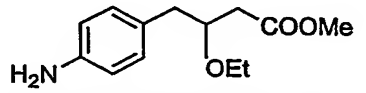
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.22 (t, J=7 Hz, 3H); 1.27 (t, J=7 Hz, 3H); 1.60-1.80 (m, 4H); 2.52 (t, J= 6.8 Hz, 2H); 3.30-3.50 (m, 1H); 3.50-3.70 (m, 1H); 3.82 (d, J= 5.3 Hz, 1H); 4.19 (q, J=7 Hz, 2H); 6.62 (d, J=8.3 Hz, 2H); 6.96 (d, J=8.3 Hz, 2H).

IR (neat) cm^{-1}: 3457, 2931, 1747, 1626, and 1517.

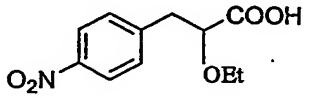
Mass m/z(CI): 265 [M], 266 [M + 1].

Preparation 20

Methyl 3-ethoxy-4- (4-aminophenyl) butanoate

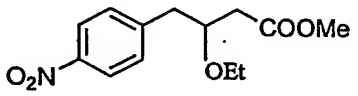


Step: 1 **2-ethoxy-3- (4-nitrophenyl) propanoic acid**



Ethyl 2-ethoxy-3-(4-nitrophenyl)propanoate (5 g, 1.0 eq, 18.72 mmol), prepared from 4-nitro phenyl alanine was hydrolyzed by treating with $LiOH.H_2O$ (1.18 g, 1.5 eq, 28.08 mmol) in MeOH-THF-water solvent mixture at RT for 3-4 h. The reaction mixture was condensed, diluted with water and acidified (pH at 3) with aq. HCl. Desired acid was extracted with ethyl acetate (200 mL). Organic layer was dried (Na_2SO_4), condensed, and the crude (3.66 g, 82 % yield) was directly used for next reaction.

Step 2: **Methyl 3-ethoxy-4- (4-nitrophenyl) butanoate**



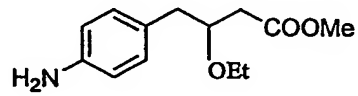
To a stirred solution of 2-ethoxy-3- (4-nitrophenyl) propanoic acid (3.6 g, 1 eq, 15.10 mmol), obtained in **step 1 of preparation 20**, and Et_3N (2.1 mL, 1 eq, 15.10 mmol) in dry DCM (75 mL), isobutyl chloroformate (1.97 mL) was added at 0 °C, and stirring was continued at RT for 1 h. Then at -5 °C, CH_2N_2 (generated in 40mL of diethyl ether) was added drop wise. After the addition, reaction was continued for 1 h at 0 °C. Reaction mixture was diluted with DCM (50 mL), and washed with water. Organic layer was dried (Na_2SO_4), condensed, and dried under high vac. The crude mass thus obtained (3.9 g, 1eq, 14.8 mmol) was dissolved in MeOH (80 mL) and Et_3N (6.2 mL, 3 eq, 44.4 mmol) was added. After the addition, Silver acetate (2.5 g, 1 eq, 14.8 mmol) was added at 0 °C in portions and stirring was continued for 1 h. Reaction mixture was condensed to dryness and the crude mass was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass. (2 g, 51 % yield).

^1H NMR ($CDCl_3$, 400 MHz) δ: 1.07 (t, J= 6.8 Hz, 3H); 2.42 (dd, J=15.6, 6.4 Hz, 1H); 2.56 (dd, J=15.6, 7 Hz, 1H); 2.87-2.98 (m, 2H); 3.33-3.41 (m, 1H); 3.47-3.55 (m, 1H); 3.69 (s, 3H); 3.96 (q, 1H); 7.4 (d, J=8.8 Hz, 2H); 8.15 (d, J=8.8 Hz, 2H).

IR (neat) cm^{-1}: 2976, 1738, 1603, and 1520.

Mass m/z(CI): 268 [M+1]

Step 3: **Methyl 3-ethoxy-4- (4-aminophenyl) butanoate**



A solution of Methyl 3-ethoxy-4- (4-nitrophenyl) butanoate (2 g, 1 eq, 7.49 mmol) obtained in step 2 of preparation 20 and 10 % Pd/C (500 mg) in ethyl acetate (250 mL) was hydrogenated at 40 psi H_2 pressure and at RT for 7 h. Reaction mixture

was filtered through celite, dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (1.3 g, 73 % yield).

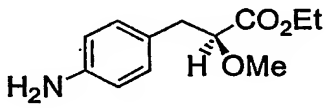
^{1}H NMR ($CDCl_3$, 400 MHz) δ:1.13 (t, J=7 Hz, 3H); 2.44 (d, J=6.2 Hz, 2H); 2.62 (dd, J=13.8, 7 Hz, 1H); 2.82 (dd, J=13.8, 5.8 Hz, 1H); 3.31-3.55 (m, 2H + NH); 3.65 (s, 3H); 3.85-3.94 (m, 1H); 6.62 (d, J= 7.8 Hz, 2H); 7 (d, J=7.8 Hz, 2H).

IR (neat) cm^{-1}: 3370, 2975, 1736, 1626, and 1518.

Mass m/z(CI): 238 [M+1]

Preparation 21

(*S*)-Ethyl 2-methoxy-3-(4-aminophenyl)propionate



Step 1: To a solution of (*S*)-(4-nitrophenyl) glycine (10g, 47.6 mmol) in a mixture of water (50 mL), H_2SO_4 (1M, 60 mL) and acetone (150 mL) at –5 °C, was added under stirring, a solution of sodium nitrite (9.85g, 142.8 mmol) in water (40 mL) drop wise over a period of 30 min. The reaction mixture was stirred at –5 to 0 °C for another 1.5 h, followed by stirring at room temperature for 16 h. Acetone was removed and then the reaction mixture was diluted with 500 mL ethyl acetate. Organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude mass was purified by crystallization from isopropyl acetate (9.0 g, 96 %).

Mp: 134-136 °C

$[\alpha]_D$: -25° (c 1.0, MeOH)

^{1}H NMR ($CDCl_3$) δ : 3.04 (dd, J = 14, 7.8 Hz, 1H), 3.24 (dd, J = 14, 4, Hz, 1H), 4.39 (dd, J = 7.3, 4.1 Hz, 1H), 7.42 (d, J = 8.7 Hz, 2H), 8.16 (d, J = 8.7 Hz, 2H).

IR (neat) cm^{-}1: 3485, 3180, 2927, 1715, 1515, 1343.

Mass m/z (CI) : 212 (M+1).

Step 2: (*S*)-2-Hydroxy-3-(4-nitrophenyl)propionic acid (9.0 g, 42.6 mmol), obtained from step (1) above, was dissolved in dry EtOH (300 mL). To this solution was added conc. H_2SO_4 (326 μL, 5.9 mmol), and refluxed for 5 to 6 h. The reaction mixture was neutralized with aqueous sodium bicarbonate. Ethanol was condensed on rotavapor, and the residue was dissolved in ethyl acetate. Organic layer was washed with aqueous sodium bicarbonate, water, brine, and then dried over anhydrous Na_2SO_4, and concentrated. Desired product was obtained from the crude mass by crystallizing from diisopropylether (8.0 g, 78.5 %)..

Mp: 74-76 °C.

$[\alpha]_D$: -13° (c 1.0, MeOH)

^1H NMR ($CDCl_3$) δ : 1.30 (t, J = 7 Hz, 3H), 3.06 (dd, J = 14, 7, Hz, 1H), 3.25 (dd, J = 14, 4.3, Hz, 1H), 4.25 (q, J = 7 Hz, 2H), 4.25 (dd, J = 7, 4.3 Hz, 1H), 7.42 (d, J = 8.7 Hz, 2H), 8.16 (d, J = 8.7 Hz, 2H).

IR (neat) cm^{-1}: 3432, 2924, 1736, 1518, 1347.

Mass m/z (CI): 240 (M+1).

Step 3: To a mixture of (*S*)-Ethyl 2-Hydroxy-3-(4-nitrophenyl)propionate (12.5 g, 52.3 mmol), obtained in step (ii) of above, and powdered Ag_2O (36.3 g, 157 mmol) in dry acetonitrile (260 mL) was added methyl iodide (13 mL, 209.2 mmol) at room temperature. Activated molecular sieves (4 A) (12.5 g) were added and then the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through celite, and concentrated. The crude mass was chromatographed using ethyl acetate and hexanes to obtain the desired product as viscous liquid (10.0 g, 75%).

$[\alpha]_D$: -30.1° (c 1.0, MeOH)

^1H NMR ($CDCl_3$) δ : 1.24 (t, J = 7.1 Hz, 3H); 3.09 (d, J = 5.4 Hz, 1H); 3.12 (d, J = 2.7 Hz, 1H); 3.35 (s, 3H); 3.96 (dd, J = 7.5, 5.1 Hz, 1H); 4.19 (q, J = 7.1 Hz, 2H); 7.39 (d, J = 8.6 Hz, 2H); 8.13 (d, J = 8.6 Hz, 2H).

IR (neat) cm^{-1}: 2995, 1747, 1604, 1521, 1343.

Mass m/z (CI): 254 (M+1).

Step 4: (*S*)-Ethyl 2-methoxy-3-(4-nitrophenyl)propionate (8.0, 31.6 mmol), obtained in step (3) above, was dissolved in dry methanol (200 mL). To this solution was

added 10% Pd/C (2.5 g), and hydrogenated using hydrogen gas (20 psi) for 3-4 h. The reaction mixture was filtered through celite, and concentrated to a syrupy mass. After column chromatography using ethyl acetate / hexanes the desired product was isolated as thick liquid (7.0 g, quantitative).

$[\alpha]_D$: -14.1° (c 1.0, MeOH).

Chiral HPLC: >98 % ee.

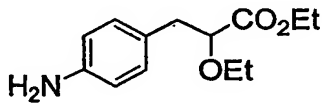
^{1}H NMR ($CDCl_3$) δ: 1.23 (t, J = 7.2Hz, 3H), 2.91 (d, J = 6.1Hz, 2H), 3.30 (bs, 2H, NH_2), 3.34 (s, 3H), 3.88 (t, J = 6.2Hz, 1H), 4.17 (q, J = 7.2Hz, 2H), 6.62 (d, J = 8.3Hz, 2H), 7.01 (d, J = 8.1Hz, 2H).

IR (neat) cm^{-1}: 3372, 2985, 2932, 1739, 1627, 1519.

Mass m/z (CI): 223 (M), 234 (M+1), 192 (M - OMe).

Preparation 22

Ethyl 2-ethoxy-3-(4-aminophenyl)propionate



Step 1: Wittig salt from triethyl 2-ethoxyphosphonoacetate (26.5 g, 1.5 eq, 99.3 mmol) and NaH (50% in oil) (5.3 g, 2 eq, 132.4 mmol) was prepared in THF (350 mL) at 0 °C. To this solid 4-nitrobenzaldehyde (10 g, 1 eq, 66.2 mmol) was added in portions at 0 °C and the resulting solution was stirred at RT for 16 h. The reaction mixture was diluted with ethyl acetate and washed with aqueous NH_4Cl. The crude contains ethyl *p*-nitro-2-ethoxycinnamate in both Z and E stereoisomers (11 g).

Step 2: Ethyl *p*-nitro-2-ethoxycinnamate obtained in step (1) was hydrogenated using 10% Pd-C - H_2 (60 psi) (11 g) in ethyl acetate (150 mL) at room temperature and chromatographed using ethyl acetate / hexane to yield the title compound as viscous oil (9.41 g, 60%).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.16 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.0 Hz, 3H), 2.90 (d, J = 6.3 Hz, 2H), 3.30 (bs, 2H, NH_2), 3.35 (m, 1H), 3.55 (m, 1H),

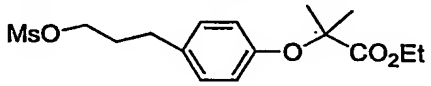
3.94 (t, J = 6.3 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 6.62 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 8.0Hz, 2H).

IR (neat) cm^{-1}: 3372, 1738.

Mass m/z (CI): 238 (M+1), 192 (M - OC_2H_5).

Preparation 23

Ethyl-2-[4-(3-methanesulphonyloxy-propyl)-phenoxy]-2-methyl-propanoate



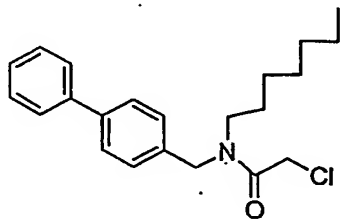
Step 1: To 3(4-hydroxy phenyl)propanol (ref: J.Org.Chem., 1998, 63(3), 889-894.)(1.57g, 10.33 mmol) in dry DMF (50mL) was added K_2CO_3 (4.3g, 31mmol) and stirred for 15 min. at room temperature and then was added ethyl-2-bromoisobutyrate (1.84mL, 12.4 mmol) follwed by Bu_4NBr (3.3g, 10.24 mmol)and the mixture was stirred at 80°C for 15h. and cooled the mixture, filtered off and washed the K_2CO_3 cake with ethyl acetate (300mL) the combined filtrates were washed with water thrice and then with brine, dried over Na_2SO_4 and evaporated the ethyl acetate to get ethyl-2-[4-(3-hydroxy-propyl)-phenoxy]-2-methyl-propanoate (1.42g, 56%) as a gummy mass which was pure enough to continue next step.

^1H NMR (δ, $CDCl_3$, 200MHz): 7.05 (d, J=8.30Hz, 2H), 6.77 (d, J=8.30Hz, 2H), 4.23 (q, J=7.08Hz, 2H), 3.66 (t, J=6.60Hz, 2H), 2.63 (t, J=7.57Hz, 2H), 1.95-1.85 (m, J=2H), 1.57 (s, 6H), 1.26 (t, J=7.80Hz, 3H).

Step 2: To ethyl-2-[4-(3-hydroxy-propyl)-phenoxy]-2-methyl-propanoate (630mg, 2.47 mmol) obtained in step (1) was dissolved in dry dichloromethane (13mL), was cooled to 0°C and added triethyl amine (0.865 mL, 6.17 mmol) under nitrogen atmosphere followed by methane sulphonyl chloride (0.3mL, 3.71mmol) and the mixture was stirred at room temperature for about 3h. The mixture was diluted with 100mL of dichloromethane and washed thrice with 100mL of water, brine, dried over Na_2SO_4 and evaporated the solvent to give ethyl-2-[4-(3-methanesulphonyloxy-propyl)-phenoxy]-2-methyl-propanoate (0.808g, 99%) as gummy mass.

Preparation 24

N-biphenyl-4-yl-methyl-2-chloro-N-heptyl-acetamide

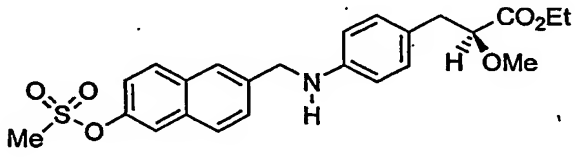


To the biphenyl-4-yl-methyl-heptylamine (1g, 3.55mmol) in dichloromethane (20mL) was added triethyl amine (1.23mL, 8.87 mmol) cooled the reaction mixture to 0^0C and then was added chloroacetyl chloride (0.6mL, 5.32mmol) the resulting mixture was stirred at room temperature for 12h, diluted with more (100mL) of dichloromethane, washed with water, brine and dried over Na_2SO_4, evaporated the solvent to give a colorless viscous liquid of N-biphenyl-4-yl-methyl-2-chloro-N-heptyl-acetamide (1.3g, 100%).

^{1}H NMR (δ, $CDCl_3$, 200MHz):7.60-7.20 (m, 9H), 4.65 (s, 2H), 4.16 (s, 3H), 3.41 (t, J=7.51Hz, 2H), 1.40-1.20 (bs, 10H), 0.88 (t, J=6.10Hz, 3H).

Example 1

(S)-Ethyl 2-methoxy-3- [4-{6-methanesulfonyloxynapth-2-ylmethylamino} phenyl] propanoate



A mixture of 6-methanesulfonyloxynapthyl-2-carboxaldehyde (500 mg, 1 eq, 2 mmol) obtained in preparation 1, *S* ethyl 2-methoxy-3-(4-aminophenyl)propionate (446 mg, 1 eq, 2 mmol), (obtained in preparation 21), activated molecular sieves (4 A), and p-TsOH (38 mg, 0.1 eq, 0.2 mmol) in dry DCM (5 mL) were stirred at RT for 16 h. The reaction mixture was diluted with ethyl acetate (100 ml), washed with aq. sodium bicarbonate, dried (Na_2SO_4), condensed (rotavapor), and dried under high vac. The crude mass (825 mg) was dissolved in dry methanol (10 ml) and conc HCl (181 µL) was added at 0 °C, followed by $NaB(CN)H_3$ (172 mg, 1.5 eq, 2.727 mmol) in portions. The reaction mixture was stirred at 0 °C for 3 h, after that it was diluted with ethyl acetate (100 mL). The organic layer was washed with aq. sodium bicarbonate,

dried (Na_2SO_4), and condensed. The residue was chromatographed using ethyl acetate and hexanes to obtain the title compound as white solid (560 mg, 68 % yield). Mp: 94-96°C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.21 (t, J=7.0 Hz, 3H); 2.8-2.9 (m, 2H); 3.18 (s, 3H); 3.34 (s, 3H); 3.88 (dd, J=7.3, 6 Hz, 1H); 4.16 (q, J=7.0 Hz, 2H); 4.49 (s, 2H); 6.58 (d, J=8.3 Hz, 2H); 7.03 (d, J=8.3 Hz, 2H); 7.39 (dd, J=8.8, 2.4 Hz, 1H); 7.54 (dd, J=8.3, 1.4 Hz, 1H); 7.74 (d, J=2 Hz, 1H); 7.81-7.85 (aromatics, 3H).

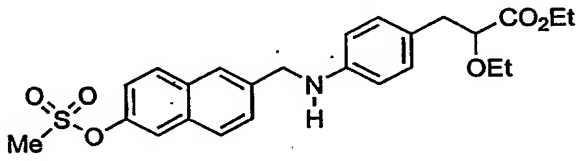
IR (neat) cm^{-1}: 3380, 2927, 1727, 1614, and 1522.

Mass m/z(CI): 458 [M + 1].

The following examples **(examples 2-4)** were made using the typical procedure described for **example 1**.

Example 2

Ethyl 2-ethoxy-3- [4-{6-methanesulfonyloxynapth-2-ylmethylamino} phenyl] propanoate



White solid, Mp: 118-120°C, Yield: 520mg, 52%.

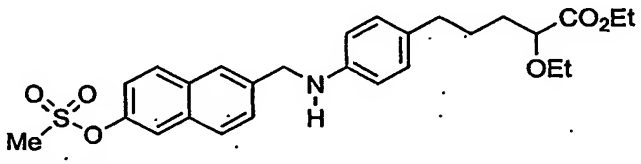
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.11-1.24 (m, 6H); 2.87 (d, J=6.7 Hz, 2H); 3.16 (s, 3H); 3.22-3.42 (m, 1H); 3.48-3.68 (m, 1H); 3.92 (t, J=6.7 Hz, 1H); 4.13 (q, J=7.0 Hz, 2H); 4.47 (s, 2H); 6.56 (d, J=8.3 Hz, 2H); 7.02 (d, J=8.3 Hz, 2H); 7.37 (dd, J=8.8, 2.4 Hz, 1H); 7.52 (d, J=8.8Hz, 1H); 7.72 (d, J=2 Hz, 1H); 7.78-7.84 (aromatics, 3H).

IR (neat) cm^{-1}: 3381, 2928, 1731, 1614, and 1522.

Mass m/z(CI): 471 [M], 472 [M + 1].

Example 3

Ethyl 2-ethoxy-5- [4-{6-methanesulfonyloxynapth-2-ylmethylamino} phenyl] pentanoate



Yield: 580mg, 72%.

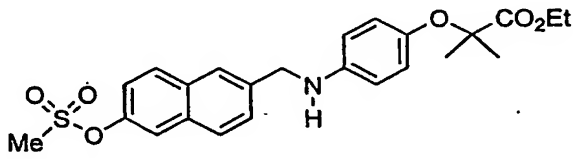
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.20 (t, J=7.4 Hz, 3H); 1.26 (t, J=7.3 Hz, 3H); 1.60-1.80 (m, 4H); 2.51 (t, J=7.3 Hz, 2H); 3.18 (s, 3H); 3.23-3.40 (m, 1H); 3.58-3.62 (m, 1H); 3.80 (t, J=6.8 Hz, 1H); 4.15-4.21 (m, 2H); 4.49 (s, 2H); 6.59 (d, J=8.8 Hz, 2H); 6.97 (d, J=8.8 Hz, 2H); 7.39 (dd, J=8.8, 2.4 Hz, 1H); 7.55 (dd, J=8.3, 1.5 Hz, 1H); 7.74 (d, J=2.4 Hz, 1H); 7.81-7.86 (aromatics, 3H).

IR (neat) cm^{-1}: 3404, 2931, 1740, 1614, and 1521.

Mass m/z (CI): 499 [M], 500 [M + 1].

Example 4

Ethyl 2-methyl-2- [4-{6-methanesulfonyloxynapth-2-ylmethylamino} phenoxy] propanoate



White solid, Mp: 116-118°C, Yield: 800 mg, 73 %.

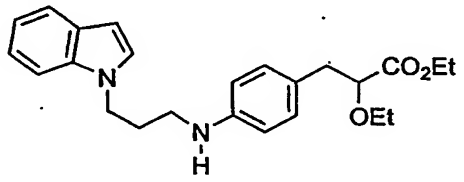
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.27 (t, J=7Hz, 3H); 1.50 (s, 6H); 3.18 (s, 3H); 4.00 (bs, NH); 4.22 (q, J=7 Hz, 2H); 4.45 (s, 2H); 6.54 (d, J=8.8 Hz, 2H); 6.77 (d, J=8.8 Hz, 2H); 7.34 (dd, J= 8.8, 2.4 Hz, 1H); 7.54 (d, J=9.6 Hz, 1H); 7.74 (d, J=2.4 Hz, 1H); 7.80-7.87 (aromatics, 3H).

IR (neat) cm^{-1}: 3409, 2987, 2936, 1731, and 1512.

Mass m/z (CI): 458 [M + 1].

Example 5

Ethyl 2-ethoxy-3- [4-{3-(indol-1-yl) propyl amino} phenyl] propanoate



A mixture of Ethyl 2-ethoxy-3- (4-aminophenyl) propanoate (450 mg, 1 eq, 1.90 mmol) (obtained in preparation 22) , 3-(indol-1-yl) propyl bromide (500 mg, 1.1 eq, 2.10 mmol) obtained in **preparation 8**, anhydrous K_2CO_3 (786 mg, 3 eq, 5.70 mmol), and TBAB (122 mg, 0.2 eq, 0.38 mmol) in dry toluene (13 mL) was stirred at 90 °C for 5 h. Reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (2x100 mL). Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound as thick mass (335 mg, 40 % yield).

^1H NMR ($CDCl_3$, 400 MHz) δ: 1.16 (t, J=7.3 Hz, 3H); 1.22 (t, J=7 Hz, 3H); 2.13 (quintet, J=6.8 Hz, 2H); 2.89 (d, J=6.3 Hz, 2H); 3.09 (t, J=7 Hz, 2H); 3.30-3.40 (m, 1H); 3.55-3.62 (m, 1H); 3.94 (t, J= 6.3 Hz, 1H); 4.16 (q, J=7 Hz, 2H); 4.26 (t, J=6.3, 2H); 6.47 (d, J=8.8 Hz, 2H); 6.49 (dd, J=10, 4 Hz, 1H); 7.03 (d, J=8.3 Hz, 2H); 7.08-7.12 (aromatics, 2H); 7.20 (dt, J=8.3, 1.5 Hz, 1H); 7.34 (d, J=8.3 Hz, 1H); 7.64 (d, J=7.8 Hz, 1H).

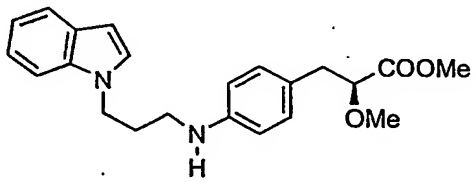
IR (neat) cm^{-1}: 3393, 2928, 1739, 1616, and 1521.

Mass m/z(CI): 395 [M + 1].

The following examples (**examples 6-14**) were made using the typical procedure described for **example 5**.

Example 6

(S)-Methyl 2-methoxy-3- [4-{3-(indol-1-yl) propylamino} phenyl] propanoate



Yield: 400mg, 52%

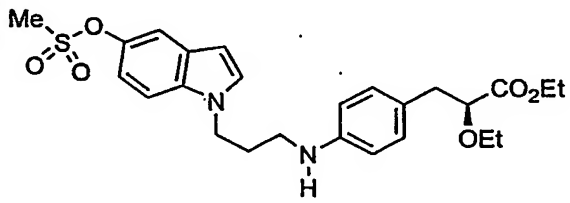
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.14 (quintet, J=6.8 Hz, 2H); 2.91 (d, J=5.9 Hz, 2H); 3.09 (t, J=6.7 Hz, 2H); 3.35 (s, 3H); 3.72 (s, 3H); 3.91 (t, J= 5.9 Hz, 1H); 4.27 (t, J=6.7, 2H); 6.45-6.55 (aromatics, 3H); 6.95-7.40 (aromatics, 6H); 7.65 (d, J=7.8 Hz, 1H).

IR (neat) cm^{-1}: 3394, 2926, 1743, 1614, and 1521.

Mass m/z (CI): 367 [M + 1].

Example 7

(S)-Ethyl-2-ethoxy-3- [4-{3-(5-methanesulfonyloxyindol-1-yl) propylamino} phenyl] propanoate



Yield: 600mg, 65%.

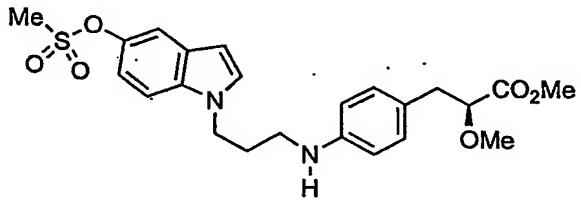
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.17 (t, J=7 Hz, 3H); 1.23 (t, J=7.3 Hz, 3H); 2.13 (quintet, J=6.9 Hz, 2H); 2.90 (d, J=6.8 Hz, 2H); 3.08 (t, J=6.8 Hz, 2H); 3.12 (s, 3H); 3.32-3.40 (m, 1H); 3.54-3.62 (m, 1H); 3.94 (d, J= 6.8 Hz, 1H); 4.16 (q, J=7 Hz, 2H); 4.26 (t, J=7 Hz, 2H); 6.47 (d, J=8.8 Hz, 2H); 6.52 (d, J=2.5 Hz, 1H); 7.03 (d, J=8.3 Hz, 2H); 7.12 (dd, J=8.8, 2.5 Hz, 1H); 7.17 (d, J=3.4 Hz, 1H); 7.32 (d, J=8.8 Hz, 1H); 7.53 (d, J=2.4 Hz, 1H).

IR (neat) cm^{-1}: 3392, 2927, 1740, 1616, and 1522.

Mass m/z (CI): 489 [M + 1].

Example 8

S)-Methyl-2-methoxy-3- [4-{3-(5-methanesulfonyloxyindol-1-yl) propylamino} phenyl] propanoate



Yield: 675mg, 76%.

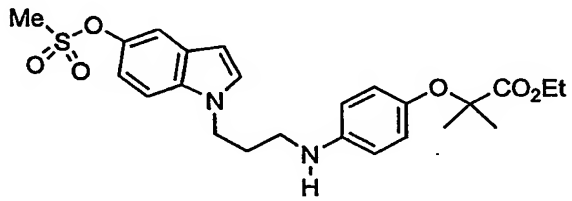
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.13 (quintet, J=6.9 Hz, 2H); 2.85-2.94 (m, 2H); 3.08 (t, J=6.8 Hz, 2H); 3.13 (s, 3H); 3.35 (s, 3H); 3.72 (s, 3H); 3.91 (dd, J= 7.4, 5.3 Hz, 1H); 4.27 (t, J=6.9 Hz, 2H); 6.49 (d, J=8.8 Hz, 2H); 6.52 (d, J=2.5 Hz, 1H); 7.02 (d, J=8.8 Hz, 2H); 7.12 (dd, J=8.8, 2.5 Hz, 1H); 7.18 (d, J=2.4 Hz, 1H); 7.33 (d, J=8.8 Hz, 1H); 7.54 (d, J=2 Hz, 1H).

IR (neat) cm^{-1}: 3404, 2929, 1742, 1616, and 1521.

Mass m/z(CI): 461 [M + 1].

Example 9

Ethyl 2-methyl-2- [4-{3-(5-methanesulfonyloxyindol-1-yl) propylamino} phenoxy] propanoate



Yield: 600mg, 54%

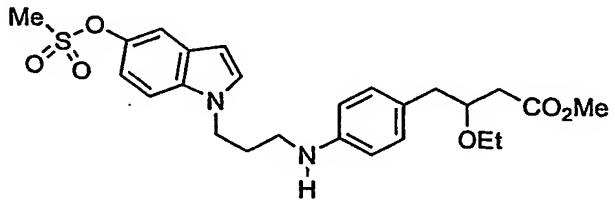
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28 (t, J=7.1 Hz, 3H); 1.50 (s, 6H); 2.11 (quintet, J=6.3 Hz, 2H); 3.05 (t, J=6.9 Hz, 2H); 3.11 (s, 3H); 4.20-4.27 (m, 4H); 6.42 (d, J=8.8 Hz, 2H); 6.51 (d, J=3 Hz, 1H); 6.76 (d, J=8.8 Hz, 2H); 7.10 (dd, J=8.8, 2.5 Hz, 1H); 7.17 (d, J=3.4 Hz, 1H); 7.31 (d, J=8.8 Hz, 1H); 7.53 (d, J=2 Hz, 1H).

IR (neat) cm^{-1}: 3399, 2935, 1730, 1611, and 1512.

Mass m/z (CI): 475 [M + 1].

Example 10

(S)-Methyl 3-ethoxy-4- [4-{3-(5-methanesulfonyloxyindol-1-yl) propylamino} phenyl] butanoate



Yield: 500mg, 49 %

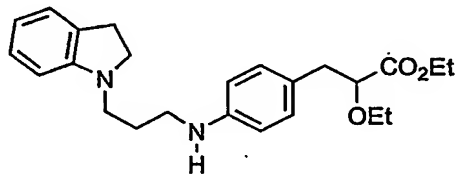
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.12 (t, J=7 Hz, 3H); 2.13 (quintet, J=6.4 Hz, 2H); 2.42 (d, J=2.4 Hz, 1H); 2.43 (d, J=4.5 Hz, 1H); 2.62 (dd, J=14, 7 Hz, 1H); 2.80 (dd, J=14, 5.8 Hz, 1H); 3.08 (t, J=6.8 Hz, 2H); 3.12 (s, 3H); 3.47-3.53 (m, 2H); 3.65 (s, 3H); 3.88 (quintet, J=5.8 Hz, 1H); 4.27 (t, J=6.7 Hz, 2H); 6.48 (d, J=8.8 Hz, 2H); 6.52 (dd, J=3, 0.7 Hz, 1H); 6.99 (d, J=8.8 Hz, 2H); 7.11 (dd, J=8.8, 2.4 Hz, 1H); 7.17 (d, J=3.4 Hz, 1H); 7.32 (d, J=8.8 Hz, 1H); 7.53 (d, J=2.1 Hz, 1H).

IR (neat) cm^{-1}: 3406, 2929, 1734, 1616, 1521.

Mass m/z(CI): 489 [M + 1].

Example 11

Ethyl 2-ethoxy-3- [4-{3-(2,3-dihydroindol-1-yl) propylamino} phenyl] propanoate



Yield: 465mg, 35%

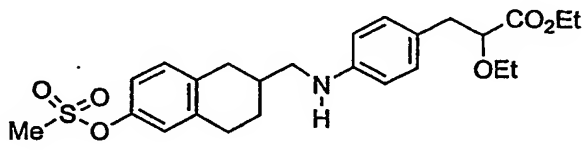
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.17 (t, J=7.3 Hz, 3H); 1.22 (t, J=6.8 Hz, 3H); 1.92 (quintet, J=6.8 Hz, 2H); 2.90 (d, J=6.8 Hz, 2H); 2.96 (t, J=6.9 Hz, 2H); 3.17 (t, J=6.9 Hz, 2H); 3.25 (t, J=6.9 Hz, 2H); 3.30-3.40 (m, 3H); 3.56-3.61 (m, 1H); 3.80 (bs, 1H); 3.94 (t, J= 6.9 Hz, 1H); 4.16 (q, J=6.8 Hz, 2H); 6.48 (d, J=7.8 Hz, 1H); 6.54 (d, J=8.3 Hz, 2H); 6.56 (t, J=7.3 Hz, 1H); 7.03-7.09 (aromatics, 4H).

IR (neat) cm^{-1}: 3398, 2926, 1742, 1610, 1522.

Mass m/z(CI): 397 [M + 1].

Example 12

Ethyl 2-ethoxy-3- [4-{(6-methanesulfonyloxy-1,2,3,4-tetrahydronapth-2-yl)methylamino}phenyl] propanoate



Yield: 100mg, 20 %

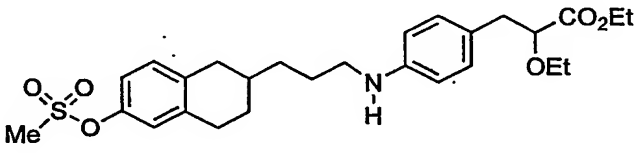
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.17 (t, J=7 Hz, 3H); 1.25 (t, J=7.2 Hz, 3H); 1.42-1.55 (m, 1H); 1.95-2.00 (m, 2H); 2.51 (dd, J= 16, 10 Hz, 1H); 2.80-3.00 (m, 5H); 3.12-3.18 (m, 5H); 3.25-3.42 (m, 1H); 3.48-3.65 (m, 1H); 3.94 (t, J=6.6 Hz, 1H); 4.16 (q, J=7.2 Hz, 2H); 6.57 (d, J=8.3 Hz, 2H); 7.90-7.15 (aromatics, 5H).

IR (neat) cm^{-1}: 2925, 1739.

Mass m/z (ES): 476 [M + 1].

Example 13

Ethyl 2-ethoxy-3- [4-{3-(6-methanesulfonyloxy-1, 2,3,4-tetrahydronapth-2-yl) propylamino} phenyl] propanoate



Yield: 125mg, 16%.

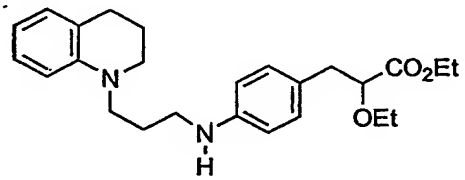
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.17 (t, J=7.1 Hz, 3H); 1.23 (t, J=7Hz, 3H); 1.20-1.60 (m, 5H); 1.72 (quintet, J=7.3 Hz, 2H); 1.90-2.00 (m, 1H); 2.40 (dd, J= 16, 10 Hz, 1H); 2.80-2.85 (m, 2H); 2.90 (d, J=6.7 Hz, 2H); 3.10-3.14 (m, 5H); 3.33-3.40 (m, 1H); 3.55-3.62 (m, 1H); 3.95 (t, J=6.7 Hz, 1H); 4.17 (q, J=7.0 Hz, 2H); 6.55 (d, J=8.3 Hz, 2H); 6.98-7.09 (aromatics, 5H).

IR (neat) cm^{-1}: 3403, 2926, 1741, 1616, and 1522.

Mass m/z(CI): 504 [M + 1].

Example 14

Ethyl 2-ethoxy-3- [4-{3-(1,2,3,4-tetrahydroquinolyn-1-yl) propylamino} phenyl] propanoate



Yield: 455mg, 43%.

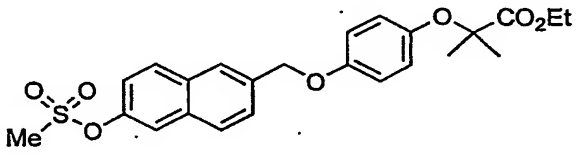
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.17 (t, J=7 Hz, 3H); 1.22 (t, J=7.2 Hz, 3H); 1.88-1.97 (m, 4H); 2.75 (t, J=6.6 Hz, 2H); 2.89 (d, J=6.8 Hz, 2H); 2.96 (t, J=6.9 Hz, 2H); 3.18 (t, J=6.9 Hz, 2H); 3.27 (t, J=6.9 Hz, 2H); 3.32-3.39 (m, 3H); 3.55-3.62 (m, 1H + NH); 3.94 (t, J=6.9 Hz, 1H); 4.16 (q, J=7.2 Hz, 2H); 6.52 (d, J=8 Hz, 2H); 6.54-6.59 (aromatics, 2H); 6.94 (dd, J=7.3, 1.5 Hz, 1H); 7.00-7.05 (aromatics, 3H).

IR (neat) cm^{-1}: 3392, 2929, 1738, 1520.

Mass m/z(CI): 411 [M + 1].

Example 15

Ethyl 2-methyl-2- [4-{6-methanesulfonyloxynapth-2-ylmethoxy} phenoxy] propanoate



A mixture of Ethyl 2-methyl-2-(4-hydroxyphenoxy) propanoate (200 mg, 1 eq, 0.89 mmol), (Ref: *J. Med. Chem.* 2001, 44, 2061) (0.350 g) 6-(methanesulfonyloxy)napth-2-ylmethyl bromide (280mg, 1eq, 0.89mmol), obtained in **preparation 2**, and anhydrous K_2CO_3 (368 mg, 3 eq, 2.67 mmol) in 5 mL dry DMF was stirred at RT for 17 h.Reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2x100 mL). Organic layer was dried (Na_2SO_4), condensed,

and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound.

Yield: 335mg, 82%.

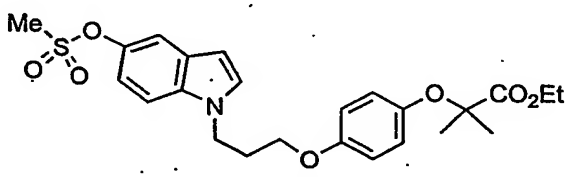
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.26 (t, J=7.2 Hz, 3H); 1.54 (s, 6H); 3.18 (s, 3H); 4.23 (q, J=7.2 Hz, 2H); 5.17 (s, 2H); 6.83-6.89 (aromatics, 4H); 7.41(dd, J=8.8, 2.4 Hz, 1H); 7.58 (dd, J=8.8, 1.6 Hz, 1H); 7.66 (d, J=2.4 Hz, 1H); 7.85-7.90 (aromatics, 3H)

IR (neat) cm^{-1}: 2986, 2936, 1730, and 1503.

Mass m/z (CI):459 [M + 1].

Example 16

Ethyl 2-methyl-2- [4-{3-(5-methanesulfonyloxyindol-1-yl) propyloxy} phenoxy] propanoate.



The compound was made using the typical procedure described for example 15 except that the reaction mixture was heated at 70 °C for 4 h.

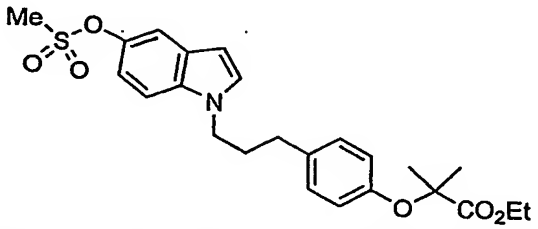
Yield: 410 mg, 57%.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28 (t, J=7.1 Hz, 3H); 1.54 (s, 6H); 2.24 (quintet, J=6.1 Hz, 2H); 3.10 (s, 3H); 3.80 (t, J=5.7 Hz, 2H); 4.24 (q, J=7.1 Hz, 2H); 4.35 (t, J=6.6 Hz, 2H); 6.48 (d, J=3 Hz, 1H); 6.74 (d, J=9.1 Hz, 2H); 6.90 (d, J=9.1 Hz, 2H); 7.08 (dd, J=8.8, 2.5 Hz, 1H); 7.15 (d, J=3 Hz, 1H); 7.33 (d, J=8.8 Hz, 1H); 7.52 (d, J=2.4 Hz, 1H).

IR (neat) cm^{-1}: 2938, 1732, 1609, and 1505.

Example 17

Ethyl 2-methyl-2- [4-{3-(5-methanesulfonyloxyindol-1-yl) propyl} phenoxy] propanoate



To a stirred solution of 5-methanesulfonyloxyindole (300 mg, 1 eq, 0.87 mmol), obtained in **step 1 of preparation 7**, and powdered KOH (50 mg, 1 eq, 0.87 mmol) in dry DMSO (4 mL) at RT for 20 min, ethyl 2-methyl-2- [4-(3-methanesulfonyloxypropyl) phenoxy] propionate (219mg, 1.2 eq, 1.04mmol); obtained in **preparation 16**, in 1 mL of dry DMSO was added at RT. And the reaction was stirred at RT for 3 h. Reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2x100 mL). Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound.

Yield: 350mg, 87%.

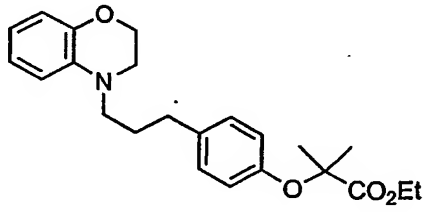
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (t, J=7.3 Hz, 3H); 1.57 (s, 6H); 2.14 (quintet, J=7.3 Hz, 2H); 2.56 (t, J=7.3 Hz, 2H); 3.12 (s, 3H); 4.10 (t, J=7 Hz, 2H); 4.24 (q, J=7.3 Hz, 2H); 6.50 (d, J=2.5 Hz, 1H); 6.79 (d, J=8.8 Hz, 2H); 7.02 (d, J=8.8 Hz, 2H); 7.11-7.15 (aromatics, 2H); 7.23 (d, J=8.8 Hz, 1H); 7.52 (d, J=3 Hz, 1H).

IR (neat) cm^{-1}: 2937, 1731, 1611, and 1509.

Mass m/z(CI): 460 [M + 1].

Example 18

Ethyl 2-methyl-2- [4-{3-(3,4-dihydro-2H-bezo [b][1,4] 0xazin-4-yl) propyl} phenoxy] propanoate



A mixture of 3,4-dihydro-2H-benz[b][1,4] oxazine (204 mg, 1 eq, 1.51 mmol), ethyl 2-methyl-2- [4-(3-iodopropyl) phenoxy] propanoate (570 mg, 1 eq, 1.51 mmol), obtained in preparation 18; and anhydrous K_2CO_3 (625 mg, 3 eq, 4.53 mmol) in dry DMF (8 mL) was stirred at 70 °C for 17 h. Reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2x100 mL). Organic layer was dried (Na_2SO_4), condensed, and the residue was chromatographed using ethyl acetate and hexane to obtain the title compound.

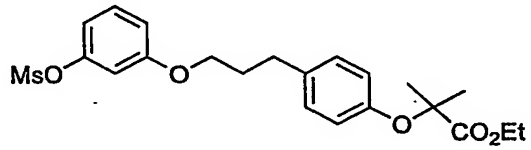
Yield: 170 mg, 30 %.

Mass m/z(CI): 484 [M + 1].

The following examples (**examples 19-22**) were made following the typical procedure of **example 18.**

Example 19

Ethyl 2-methyl-2-[4-{3-(3-methanesulfonyloxyphenoxy)propyl}phenoxy]propanoate



Yield: 500mg, 66 %.

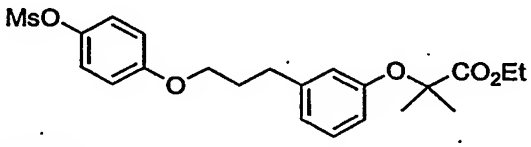
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (t, J=7 Hz, 3H); 1.57 (s, 6H); 2.04-2.08 (m, 2H); 2.73 (t, J=7.3 Hz, 2H); 3.13 (s, 3H); 3.94 (t, J=6.1 Hz, 2H); 4.23 (q, J= 7 Hz, 2H); 6.78 (d, J=8.8 Hz, 2H); 6.80-6.87 (aromatics, 3H); 7.06 (d, J=8.8 Hz, 2H); 7.28 (dd, J=8.6, 8.0 Hz, 1H).

IR (neat) cm^{-1}: 2939, 1732, 1608,1508.

Mass m/z (ES): 437 [M+1], 454 [M+18], 459 [M + 23].

Example 20

Ethyl 2-methyl-2-[3-{3-(4-methanesulfonyloxyphenoxy)propyl}phenoxy]propanoate



Yield: 400 mg, 73 %.

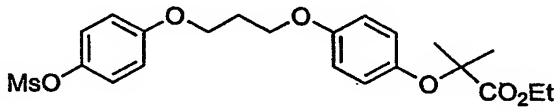
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.24 (t, J=7.2 Hz, 3H); 1.58 (s, 6H); 2.04-2.10 (m, 2H); 2.74 (t, J=7.1 Hz, 2H); 3.10 (s, 3H); 3.93 (t, J=6.2 Hz, 2H); 4.22 (q, J= 7.2 Hz, 2H); 6.66 (dd, J=8.1, 2.4 Hz, 1H); 6.73 (d, J=2.0 Hz, 1H); 6.83 (d, J=7.5 Hz, 1H); 6.88 (d, J=9.1 Hz, 2H); 7.14 (t, J= 7.8 Hz, 1H); 7.18 (d, J=9.1 Hz, 2H).

IR (neat) cm^{-1}: 2928, 1732, 1608, 1502.

Mass m/z (CI): 437 [M+1].

Example 21

Ethyl 2-methyl-2-[4-{3-(4-methanesulfonyloxyphenoxy)propyloxy}phenoxy]propanoate



Yield: 218mg, 41 %.

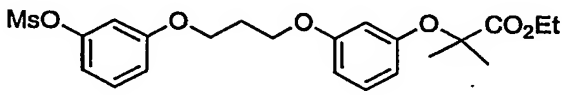
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.27 (t, J=7 Hz, 3H); 1.53 (s, 6H); 2.23 (quintet, J=6 Hz, 2H); 3.10 (s, 3H); 4.06-4.17 (m, 4H); 4.24 (q, J= 7 Hz, 2H); 6.74-6.94 (aromatics, 6H); 7.19 (d, J=9 Hz, 2H).

IR (neat) cm^{-1}: 2934, 1729, 1593,1501.

Mass m/z (CI): 453 [M+1].

Example 22

Ethyl 2-methyl-2-[3-{3-(3-methanesulfonyloxyphenoxy)propyloxy}phenoxy]propanoate



Yield: 500 mg, 68 %.

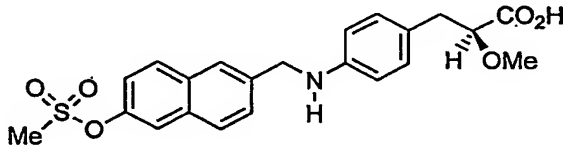
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.24 (t, J=7.2 Hz, 3H); 1.59 (s, 6H); 2.24 (quintet, J=6.2 Hz, 2H); 3.12 (s, 3H); 4.10 (t, J=6 Hz, 2H); 4.14 (t, J=6.1 Hz, 2H); 4.22 (q, J= 7.2 Hz, 2H); 6.39-6.56 (aromatics, 3H); 6.83-6.88 (aromatics, 3H); 7.11 (t, J=8 Hz, 1H); 7.29 (t, J=8.2 Hz, 1H).

IR (neat) cm^{-1}: 2936, 1732, 1603, 1486.

Mass m/z (CI): 453 [M+1].

Example 23

(*S*)-2-methoxy-3- [4-{6-methanesulfonyloxynapth-2-ylmethylamino} phenyl] propanoic acid



Ethyl 2-methoxy-3- [4-{3-(4-methanesulfonyloxyphenyl) propylamino} phenyl] propanoate (400 mg, 1.0 eq, 0.875 mmol), obtained in example 1, was hydrolyzed by treating with $LiOH.H_2O$ (55.1 mg, 1.5 eq, 1.31 mmol) in MeOH-THF-water solvent mixture at RT for 3-4 h. The reaction mixture was condensed, diluted with water and acidified (pH at 3-4) with aq. HCl. Desired acid was extracted from aqueous layer, dried (Na_2SO_4), condensed, which was then chromatographed using MeOH and $CHCl_3$ as eluents to obtain the pure acid as thick mass (150 mg, 40 % yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.92 (dd, J=14.2, 7.4 Hz, 1H); 3.05 (dd, J=14.2, 4.4 Hz, 1H); 3.18 (s, 3H); 3.40 (s, 3H); 3.97 (dd, J=7.4, 4.4 Hz, 1H); 4.49 (s, 2H); 6.62 (d, J=8.3 Hz, 2H); 7.04 (d, J=8.3 Hz, 2H); 7.39 (dd, J=8.8, 2.4 Hz, 1H); 7.55 (dd, J=8.3, 1.4 Hz, 1H); 7.74 (d, J=2 Hz, 1H); 7.80-7.85 (aromatics, 3H).

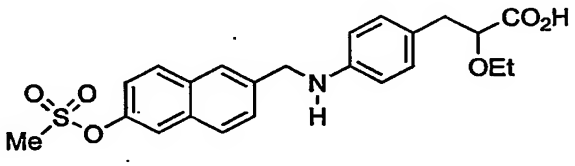
IR (neat) cm^{-1}: 3436, 2927, 1730, 1616, and 1519.

Mass m/z(ES): 430 [M + 1], 452 [M + 23]..

The following examples (**examples 24-44**) were made using the typical procedure described for **example 23**.

Example 24

2-ethoxy-3- [4-{6-methanesulfonyloxynapth-2-ylmethylamino} phenyl] propanoic acid



Mp: 168 -170 °C. Yield: 120 mg, 42 %.

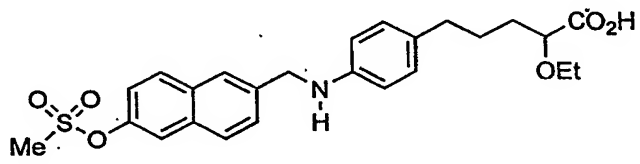
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.15 (t, J=7 Hz, 3H); 2.87 (dd, J=14.1, 7.8 Hz, 1H); 2.96 (dd, J=14.1, 4.3 Hz, 1H); 3.16 (s, 3H); 3.22-3.42 (m, 1H); 3.48-3.68 (m, 1H); 3.93 (dd, J=7.8, 4.3 Hz, 1H); 4.50 (s, 2H); 6.59 (d, J=8.3 Hz, 2H); 7.07 (d, J=8.3 Hz, 2H); 7.37 (dd, J=8.8, 2.7 Hz, 1H); 7.57 (dd, J=8.8, 1.6 Hz, 1H); 7.75 (d, J=2.7 Hz, 1H); 7.82-7.87 (aromatics; 3H).

IR (neat) cm^{-1}: 34241, 2924, and 1516.

Mass m/z (CI): 444 [M+1], 466 [M + 23].

Example 25

2-Ethoxy-5- [4-{6-methanesulfonyloxynapth-2-ylmethylamino} phenyl] pentatonic acid



Yield: 180 mg,64 %.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.23 (t, J=7.3 Hz, 3H); 1.62-1.82 (m, 4H); 2.52 (t, J=7.3 Hz, 2H); 3.18 (s, 3H); 3.47-3.55 (m, 1H); 3.58-3.64 (m, 1H); 3.88 (t, J=5.4 Hz, 1H); 4.48 (s, 2H); 6.59 (d, J=8.8 Hz, 2H); 6.97 (d, J=8.8 Hz, 2H);

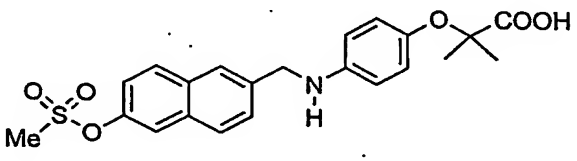
7.38 (dd, J=8.8, 2.4 Hz, 1H); 7.55 (d, J=9.7 Hz, 1H); 7.74 (d, J=1.9 Hz, 1H); 7.81-7.86 (aromatics, 3H).

IR (neat) cm^{-1}: 3409, 2926, 1724, 1613, and 1520.

Mass m/z (CI): 472 [M+1], 494 [M + 23], 943 [M_2+1]

Example 26

2-methyl-2- [4-{6-methanesulfonyloxynapth-2-ylmethylamino} phenoxy] propanoic acid



Mp: 182-184 °C. Yield: 220 mg, 47 %.

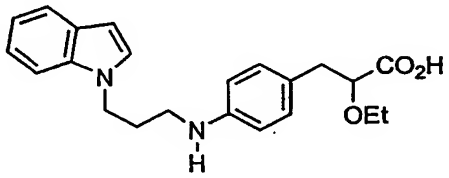
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.44 (s, 6H); 3.26 (s, 3H); 4.44 (s, 2H); 6.52 (d, J=8.8 Hz, 2H); 6.74 (d, J=8.8 Hz, 2H); 7.40 (dd, J= 8.8, 2.4 Hz, 1H); 7.58 (dd, J=8.8,1.2 Hz, 1H); 7.76 (s, 1H); 7.83-7.88 (aromatics, 3H).

IR (KBr) cm^{-1}: 3428, 2924, 2854, 1714, and 1515.

Mass m/z (ES): 430.1[M + 1], 452.1 [M+Na], 859.5 [M_2+1].

Example 27

2-ethoxy-3- [4-{3-(indol-1-yl) propyl amino} phenyl] propanoic acid



Yield: 180 mg, 71 %.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.18 (t, J=7.0 Hz, 3H); 2.14 (quintet, J=6.8 Hz, 2H); 2.89 (dd, J=14.1, 7.7 Hz, 1H); 3.03 (dd, J=14.1, 4.4 Hz, 1H); 3.08 (t, J=7. Hz, 2H); 3.44-3.50 (m, 1H); 3.55-3.60 (m, 1H); 4.03 (dd, J= 7.4, 4.4Hz, 1H); 4.27 (t, J=6.9, 2H); 6.48 (d, J=8.8 Hz, 2H); 6.50 (dd, J=10, 4 Hz, 1H); 7.03 (d,

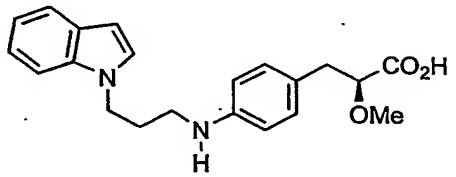
J=8.3 Hz, 2H); 7.08-7.12 (aromatics, 2H); 7.20 (dt, J=8.3, 1.5 Hz, 1H); 7.34 (d, J=8.3 Hz, 1H); 7.64 (d, J=7.8 Hz, 1H).

IR (neat) cm^{-1}: 3391, 2925, 1726, 1613, and 1519.

Mass m/z(CI): 367 [M + 1].

Example 28

(S)-2-methoxy-3- [4-{3-(indol-1-yl) propyl amino} phenyl] propanoic acid



Yield: 190 mg, 58 %.

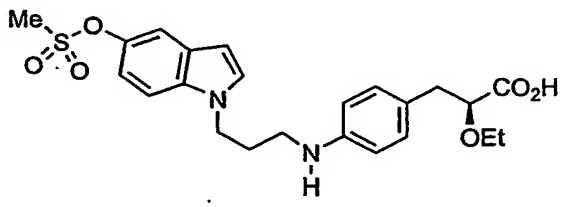
^1H NMR ($CDCl_3$, 400 MHz) δ: 2.14 (quintet, J=6.8 Hz, 2H); 2.92 (dd, J=14.1, 7.3 Hz, 1H); 3.04 (dd, J=14.1, 4.4 Hz, 1H); 3.09 (t, J=6.9 Hz, 2H); 3.39 (s, 3H); 3.96 (dd, J= 7.3, 4.4 Hz, 1H); 4.26 (t, J=6.8, 2H); 6.46-6.52 (aromatics, 3H); 7.05 (d, J=8.3 Hz, 2H); 7.08-7.13 (aromatics, 2H); 7.21 (dt, J=8.3, 1.5 Hz, 1H); 7.35 (d, J=8.3 Hz, 1H); 7.64 (d, J=7.8 Hz, 1H).

IR (neat) cm^{-1}: 3400, 2929, 1727, 1614, 1517.

Mass m/z (ES): 353 [M + 1], 375 [M+23].

Example 29

(S)-2-ethoxy-3- [4-{3-(5-methanesulfonyloxyindol-1-yl) propylamino} phenyl] propanoic acid



Yield: 400 mg, 71 %.

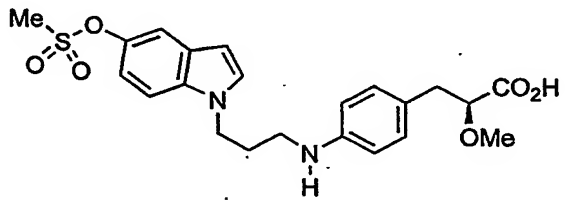
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.19 (t, J=7 Hz, 3H); 2.13 (quintet, J=6.9 Hz, 2H); 2.90 (dd, J=14.1, 7.3 Hz, 1H); 2.97 (dd, J=14.1, 4.4 Hz, 1H); 3.08 (t, J=6.8 Hz, 2H); 3.12 (s, 3H); 3.44-3.62 (m, 2H); 4.04 (dd, J= 7.3, 4.4 Hz, 1H); 4.26 (t, J=7 Hz, 2H); 6.47 (d, J=8.8 Hz, 2H); 6.52 (d, J=2.5 Hz, 1H); 7.03 (d, J=8.3 Hz, 2H); 7.12 (dd, J=8.8, 2.5 Hz, 1H); 7.17 (d, J=3.4 Hz, 1H); 7.31 (d, J=8.8 Hz, 1H); 7.53 (d, J=2.4 Hz, 1H).

IR (neat) cm^{-1}: 3400, 2930, 1729, 1615, and 1520.

Mass m/z (ES): 461 [M + 1], 483 [M+23].

Example 30

(S)-2-methoxy-3- [4-{3-(5-methanesulfonyloxyindol-1-yl) propylamino} phenyl] propanoic acid



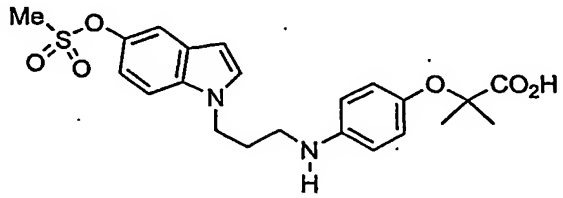
Yield: 420 mg, 65 %.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.11 (quintet, J=6.9 Hz, 2H); 2.91 (dd, J=14.2, 6.8 Hz, 1H); 3.02 (dd, J=14.2, 4.4 Hz, 1H); 3.07 (t, J=6.8 Hz, 2H); 3.11 (s, 3H); 3.39 (s, 3H); 3.95 (dd, J= 6.8, 4.4 Hz, 1H); 4.25 (t, J=6.9 Hz, 2H); 6.47 (d, J=8.8 Hz, 2H); 6.51 (d, J=2.5 Hz, 1H); 7.02 (d, J=8.8 Hz, 2H); 7.10 (dd, J=8.8, 2.5 Hz, 1H); 7.16 (d, J=2.4 Hz, 1H); 7.30 (d, J=8.8 Hz, 1H); 7.52 (d, J=2.4 Hz, 1H).

IR (neat) cm^{-1}: 3381, 2930, 1732, 1614, and 1521.

Example 31

2-methyl-2- [4-{3-(5-methanesulfonyloxyindol-1-yl) propylamino} phenoxy] propanoic acid



Mp: 164-166 °C. Yield: 300 mg, 58 %.

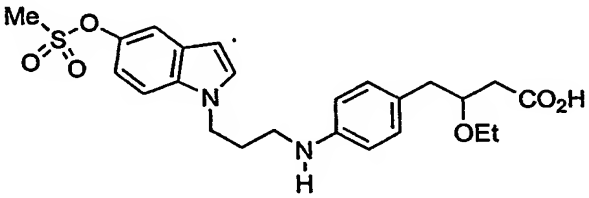
^{1}H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz) δ: 1.43 (s, 6H); 2.09 (quintet, J=6.7 Hz, 2H); 2.99 (t, J=6.8 Hz, 2H); 3.19 (s, 3H); 4.30 (t, J=6.9 Hz, 2H); 6.44 (d, J=8.8 Hz, 2H); 6.48 (d, J=3.2 Hz, 1H); 6.73 (d, J=8.8 Hz, 2H); 7.07 (dd, J=8.8, 2.7 Hz, 1H); 7.33 (d, J=3.2 Hz, 1H); 7.43 (d, J=8.8 Hz, 1H); 7.49 (d, J=2.5 Hz, 1H).

IR (neat) cm^{-1}: 3400, 2932, 1590, 1611, and 1510.

Mass m/z (ES): 447 [M + 1], 469 [M + 23], 893 [M_2 + 1].

Example 32

(S)-3-ethoxy-4- [4-{3-(5-methanesulfonyloxyindol-1-yl) propylamino} phenyl] butanoic acid



Yield: 300 mg, 61 %.

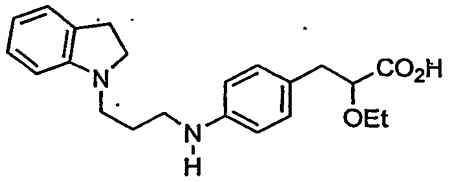
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.18 (t, J=7 Hz, 3H); 2.13 (quintet, J=6.4 Hz, 2H); 2.45-2.49 (m, 2H); 2.63 (dd, J=14, 7 Hz, 1H); 2.86 (dd, J=14, 5.8 Hz, 1H); 3.09 (t, J=6.9 Hz, 2H); 3.12 (s, 3H); 3.52-3.63 (m, 2H); 3.84-3.87 (m, 1H); 4.27 (t, J=6.8 Hz, 2H); 6.48 (d, J=8.8 Hz, 2H); 6.52 (d, J=3.4 Hz, 1H); 6.98 (d, J=8.8 Hz, 2H); 7.12 (dd, J=8.8, 2.4 Hz, 1H); 7.18 (d, J=3 Hz, 1H); 7.32 (d, J=8.8 Hz, 1H); 7.54 (d, J=2.1 Hz, 1H).

IR (neat) cm^{-1}: 3384, 2933, 1712, 1615, and 1520.

Mass m/z (ES): 475 [M + 1], 497 [M + 23].

Example 33

2-ethoxy-3- [4-{3-(2,3-dihydroindol-1-yl) propylamino} phenyl] propanoic acid



Yield: 280 mg, 72 %.

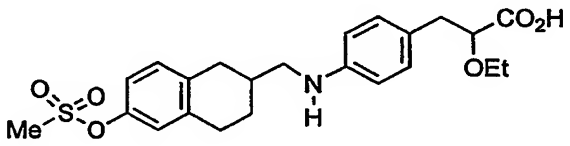
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.17 (t, J=7.3 Hz, 3H); 1.92 (quintet, J=6.8 Hz, 2H); 2.89 (dd, J=14.2, 7.8 Hz, 1H); 2.96 (t, J=8.3 Hz, 2H); 3.02 (dd, J=14.2, 3.9 Hz, 1H); 3.17 (t, J=6.9 Hz, 2H); 3.24 (t, J=6.9 Hz, 2H); 3.34 (t, J=8.3 Hz, 2H); 3.42-3.50 (m, 1H); 3.53-3.61 (m, 1H); 4.02 (dd, J=7.8, 3.9 Hz, 1H); 6.48 (d, J=7.8 Hz, 1H); 6.55 (d, J=8.3 Hz, 2H); 6.66 (dt, J=7.3, 1 Hz, 1H); 7.03-7.09 (aromatics, 4H).

IR (neat) cm^{-1}: 3391, 2927, 1725, 1607, and 1520.

Mass m/z (CI): 369 [M + 1].

Example 34

2-ethoxy-3- [4-{(6-methanesulfonyloxy-1,2,3,4-tetrahydronapth-2-yl)methylamino}phenyl] propanoic acid



Yield: 55 mg, 58 %.

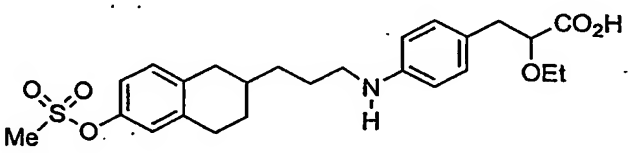
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.19 (t, J=7Hz, 3H); 1.42-1.55 (m, 1H); 2.00-2.15 (m, 2H); 2.52 (dd, J= 16, 10 Hz, 1H); 2.80-3.15 (m, 7H); 3.12 (s, 3H); 3.42-3.60 (m, 2H); 4.04 (dd, J=7.3, 4.3 Hz, 1H); 6.58 (d, J=8.3 Hz, 2H); 7.03-7.12 (aromatics, 5H).

IR (neat) cm^{-1}: 3500, 2927, and 1728.

Mass m/z (ES): 448 [M + 1], 470 [M+23].

Example 35

2-ethoxy-3- [4-{3-(6-methanesulfonyloxy-1, 2,3,4-tetrahydronapth-2-yl) propylamino} phenyl] propanoic acid



Yield: 75 mg, 69 %.

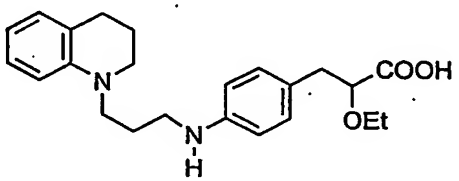
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.15 (t, J=7Hz, 3H); 1.20-1.80 (m, 7H); 1.82-2.00 (m, 1H); 2.40 (dd, J= 16, 10 Hz, 1H); 2.75-2.85 (m, 2H); 2.85-3.10 (m, 2H); 3.10-3.20 (m, 4H); 3.45-3.55 (m, 1H); 3.55-3.70 (m, 2H); 4.0 5 (dd, J=7.4, 4.4 Hz, 1H); 6.68 (d, J=8.3 Hz, 2H); 6.98-7.09 (aromatics, 5H).

IR (neat) cm^{-1}: 3503, 2928, and 1694.

Mass m/z (CI): 476 [M + 1], 498 [M+23].

Example 36

2-ethoxy-3- [4-{3-(1,2,3,4-tetrahydroquinolyn-1-yl) propylamino} phenyl] propanoic acid



Yield: 215 mg, 58 %.

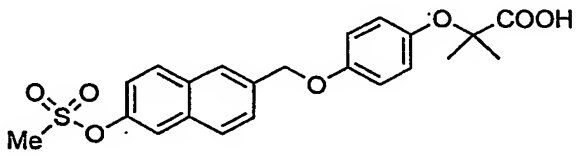
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.18 (t, J=7 Hz, 3H); 1.90-1.96 (m, 4H); 2.75 (t, J=7 Hz, 2H); 2.89 (dd, J=14, 7 Hz, 1H); 3.03 (dd, J=14, 4 Hz, 1H); 3.18 (t, J=7 Hz, 2H); 3.27 (t, J=6.9 Hz, 2H); 3.37 (t, J=7 Hz, 2H); 3.42-3.50 (m, 1H); 3.50-3.60 (m, 1H); 4.02 (dd, J=7, 4 Hz, 1H); 6.53-6.59 (aromatics, 4H); 6.94 (d, J=7.3 Hz, 1H); 7.00-7.06 (aromatics, 3H).

IR (neat) cm^{-1}: 3400, 2928, 1725, 1601.

Mass m/z(CI): 383 [M + 1].

Example 37

2-Methyl-2- [4-{6-methanesulfonyloxynapth-2-ylmethoxy} phenoxy] propanoic acid



Mp: 147-149 °C. Yield: 98 mg, 36 %.

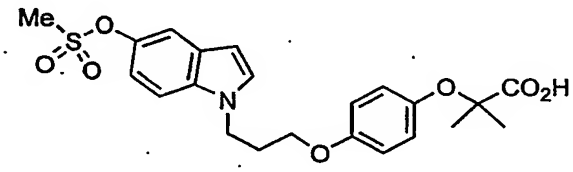
^{1}H NMR ($CDCl_3$, 400 MHz)) δ: 1.53 (s, 6H); 3.22 (s, 3H); 5.18 (s, 2H); 6.86-6.93 (aromatics, 4H); 7.40-7.43(aromatics, 2H); 7.60 (d, J=8 Hz, 1H); 7.86-7.92 (aromatics, 3H)

IR (neat) cm^{-1}: 3430, 2924, 1715, and 1504.

Mass m/z (CI):448.3 [M + NH_4], 878.5 [M_2+NH_4].

Example 38

2-methyl-2- [4-{3-(5-methanesulfonyloxyindol-1-yl) propyloxy} phenoxy] propanoic acid



Yield: 300 mg, 85 %.

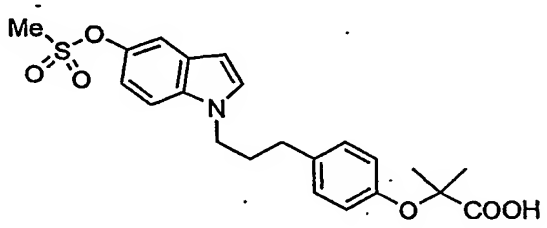
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.54 (s, 6H); 2.26 (quintet, J=6 Hz, 2H); 3.12 (s, 3H); 3.82 (t, J=5.6 Hz, 2H); 4.37 (t, J=6.4 Hz, 2H); 6.49 (d, J=3 Hz, 1H); 6.77 (d, J=8.8 Hz, 2H); 6.91 (d, J=8.8 Hz, 2H); 7.08 (dd, J=8.8, 2.4 Hz, 1H); 7.15 (d, J=3.3 Hz, 1H); 7.32 (d, J=8.8 Hz, 1H); 7.51 (d, J=2.1 Hz, 1H).

IR (neat) cm^{-1}: 3400, 2937, 1717, 1611, and 1505.

Mass m/z(ES): 448 [M + 1], 470 [M + 23].

Example 39

2-methyl-2- [4-{3-(5-methanesulfonyloxyindol-1-yl) propyl} phenoxy] propanoic acid



Yield: 170 mg, 52 %.

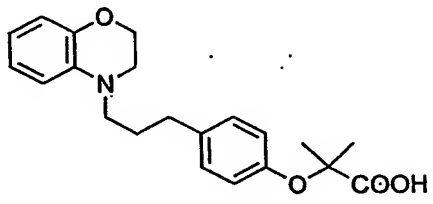
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.57 (s, 6H); 2.16 (quintet, J=7.3 Hz, 2H); 2.58 (t, J=7.7 Hz, 2H); 3.12 (s, 3H); 4.12 (t, J=7 Hz, 2H); 6.50 (d, J=2.7 Hz, 1H); 6.87 (d, J=8.6 Hz, 2H); 7.05 (d, J=8.6 Hz, 2H); 7.09-7.15 (aromatics, 2H); 7.22 (d, J=8.8 Hz, 1H); 7.52 (d, J=2.4 Hz, 1H).

IR (neat) cm^{-1}: 3326, 2937, 1716, 1609, and 1508.

Mass m/z(CI): 432 [M + 1].

Example 40

2-methyl-2- [4-{3-(3,4-dihydro-2H-bezo [b][1,4] 0xazin-4-yl) propyl} phenoxy] propanoic acid



Yield: 70 mg, 45 %.

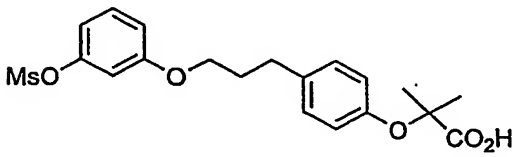
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.47 (s, 6H); 1.78 (quintet, J=7.5 Hz, 2H); 2.55 (t, J=7.6 Hz, 2H); 3.20-3.30 (m, 4H); 4.13 (t, J=4.3 Hz, 2H); 6.47 (dt, J=Hz, 1H); 6.56 (dd, J=Hz, 1H); 6.63 (dd, J=Hz, 1H); 6.67-6.73 (aromatics, 1H); 6.76 (d, J=8.6 Hz, 2H); 7.11 (d, J=8.6 Hz, 2H).

IR (neat) cm^{-1}: 3400, 2932, 1715, 1606, and 1506.

Mass m/z(ES): 356 [M + 1].

Example 41

2-Methyl-2-[4-{3-(3-methanesulfonyloxyphenoxy)propyl}phenoxy]propanoic acid



Yield: 260 mg, 56 %.

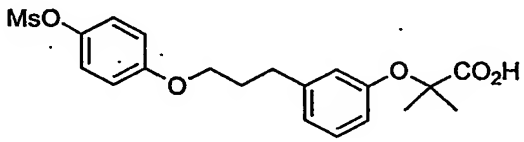
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.58 (s, 6H); 2.04-2.11 (m, 2H); 2.76 (t, J=7.3 Hz, 2H); 3.13 (s, 3H); 3.95 (t, J=6.2 Hz, 2H); 6.79-6.86 (aromatics, 3H); 6.87 (d, J=8.8 Hz, 2H); 7.11 (d, J=8.8 Hz, 2H); 7.28 (t, J=8.4 Hz, 1H).

IR (neat) cm^{-1}: 3400, 2939, 1717, 1608,1508.

Mass m/z (ES): 409 [M+1], 426 [M+18], 431 [M + 23].

Example 42

2-Methyl-2-[3-{3-(4-methanesulfonyloxyphenoxy)propyl}phenoxy]propanoic acid



Mp: 93-95 °C. Yield: 255 mg, 74 %.

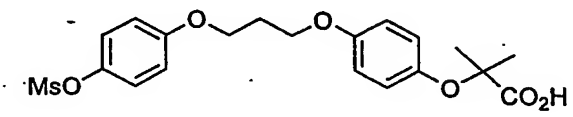
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.57 (s, 6H); 2.04-2.17 (m, 2H); 2.77 (t, J=7.1 Hz, 2H); 3.11 (s, 3H); 3.93 (t, J=6.2 Hz, 2H); 6.75-6.79 (aromatics, 2H); 6.88 (d, J=9.1 Hz, 2H); 6.92 (d, J=7.5 Hz, 1H); 7.17-7.21 (aromatics, 3H).

IR (neat) cm^{-1}: 3375, 2938, 1716, 1585,1502.

Mass m/z (ES): 409 [M+1], 426 [M+18], 431 [M + 23].

Example 43

2-Methyl-2-[4-{3-(4-methanesulfonyloxyphenoxy)propyloxy}phenoxy]propanoic acid



Yield: 115 mg, 58 %.

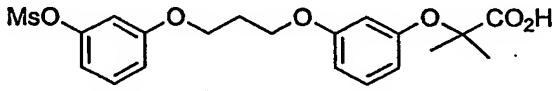
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.53 (s, 6H); 2.24 (quintet, J=6 Hz, 2H); 3.10 (s, 3H); 4.11 (t, J=6.2 Hz, 2H); 4.14 (t, J= 6.1 Hz, 2H); 6.81 (d, J=9 Hz, 2H); 6.88-6.93 (aromatics, 4H); 7.19 (d, J=9 Hz, 2H).

IR (neat) cm^{-1}: 3355, 2936, 1718, 1593,1503.

Mass m/z (ES): 425 [M+1], 442 [M+18], 447 [M+23].

Example 44

2-Methyl-2-[3-{3-(3-methanesulfonyloxyphenoxy)propyloxy}phenoxy]propanoic acid



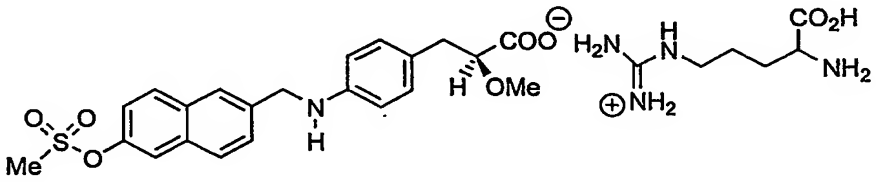
Yield: 250 mg, 59 %.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.60 (s, 6H); 2.24 (quintet, J=6 Hz, 2H); 3.12 (s, 3H); 4.11 (t, J=6 Hz, 2H); 4.14 (t, J=6.2 Hz, 2H); 6.50-6.62 (aromatics, 3H); 6.85-6.88 (aromatics, 3H); 7.14 (t, J=8 Hz, 1H); 7.29 (t, J=8.3 Hz, 1H).

IR (neat) cm^{-1}: 2936, 1732, 1603,1486.

Mass m/z (ES): 425 [M+1], 442 [M+18], 866 [M_2 + 18].

Example 45
(*S*)-2-methoxy-3- [4-{6-methanesulfonyloxynapth-2-ylmethylamino} phenyl] propanoic acid Arginine salt

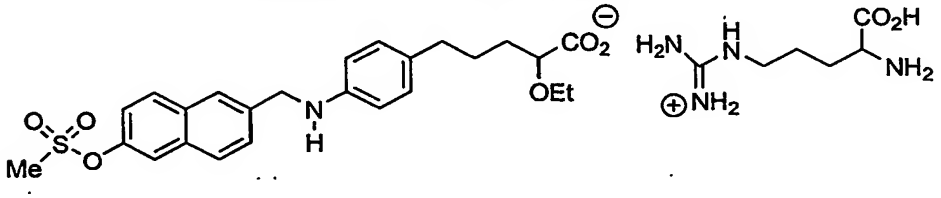


(S)-2-methoxy-3- [4-{6-methanesulfonyloxynapth-2-ylmethylamino} phenyl] propanoic acid (100 mg, 1 eq, 0.233 mmol) obtained in example 23, and L-Arginine (40.6 mg, 1 eq, 0.233 mmol) were taken in dry methanol (3 ml), and stirred at RT for 2-3 h. The solvent was removed on rotavapor followed by benzene azeotrope. The residue was dried under high vacuum pump to yield the title compound as a free flowing white solid (138 mg, yield 100 %).

Mpt: 122-124 °C.

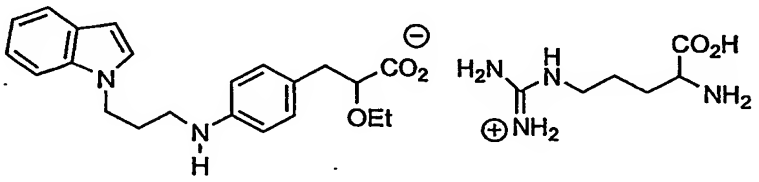
The following examples (**examples 46-61**) were made using the typical procedure described for **example 45**.

Example 46
2-Ethoxy-5- [4-{6-methanesulfonyloxynapth-2-ylmethylamino} phenyl] pentatonic acid Arginine salt



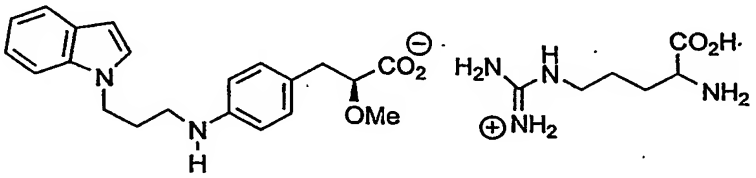
Mp: 118-120 °C.

Example 47
2-ethoxy-3- [4-{3-(indol-1-yl) propyl amino} phenyl] propanoic acid Arginine salt



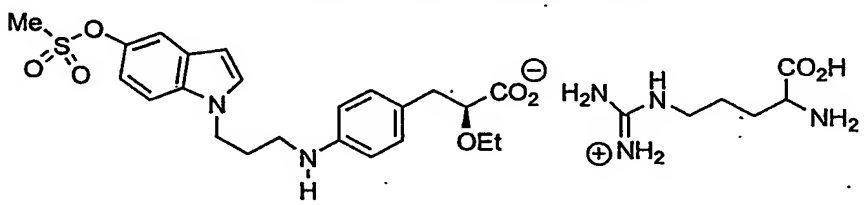
Mp: 130 °C.

Example 48
(S)-2-methoxy-3- [4-{3-(indol-1-yl) propyl amino} phenyl] propanoic acid Arginine salt



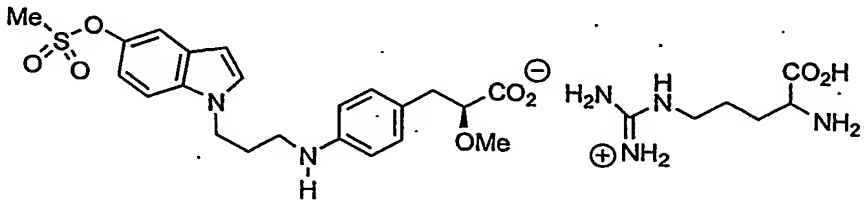
Mp: 105 °C.

Example 49
(S)-2-ethoxy-3- [4-{3-(5-methanesulfonyloxyindol-1-yl) propylamino} phenyl] propanoic acid Arginine salt



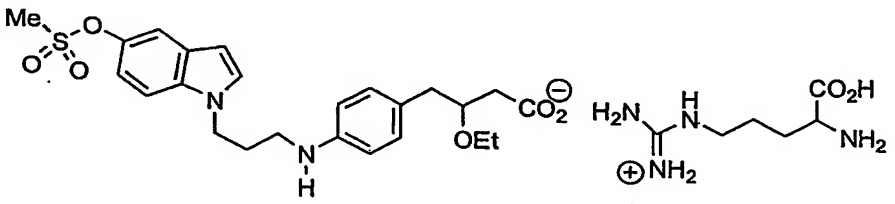
Mp: 102-104 °C.

Example 50
(S)-2-methoxy-3- [4-{3-(5-methanesulfonyloxyindol-1-yl) propylamino} phenyl] propanoic acid Arginine salt



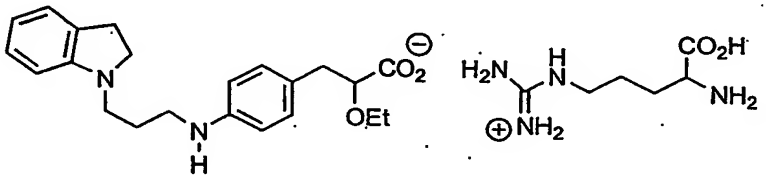
Mp: 102-104 °C.

Example 51
(S)-3-ethoxy-4- [4-{3-(5-methanesulfonyloxyindol-1-yl) propylamino} phenyl] butanoic acid Arginine salt



Mp: 98-100 °C.

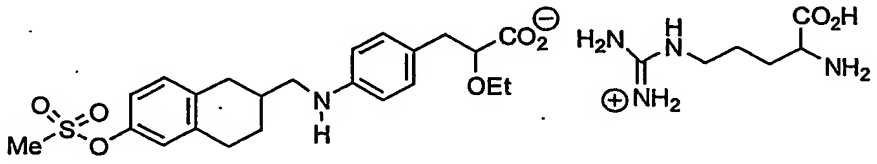
Example 52
2-ethoxy-3- [4-{3-(2,3-dihydroindol-1-yl) propylamino} phenyl] propanoic acid Arginine salt



Mp: 130-132 °C.

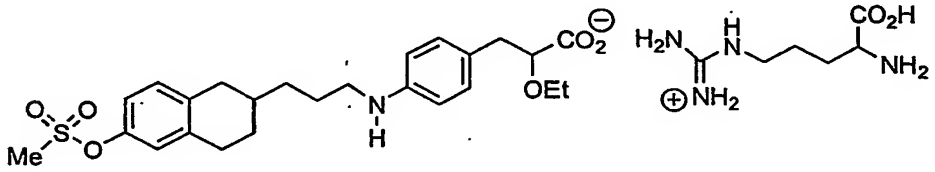
Example 53

2-ethoxy-3- [4-{(6-methanesulfonyloxy-1,2,3,4-tetrahydronapth-2-yl)methylamino}phenyl] propanoic acid Arginine salt



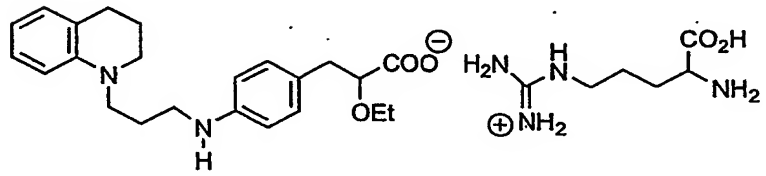
Mpt: 96-98 °C.

Example 54
2-ethoxy-3- [4-{3-(6-methanesulfonyloxy-1, 2,3,4-tetrahydronapth-2-yl) propylamino} phenyl] propanoic acid Arginine salt



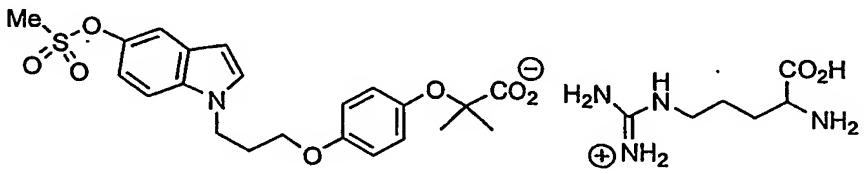
Mp: 115-117 °C.

Example 55
2-ethoxy-3- [4-{3-(1,2,3,4-tetrahydroquinolyn-1-yl) propylamino} phenyl] propanoic acid Arginine salt



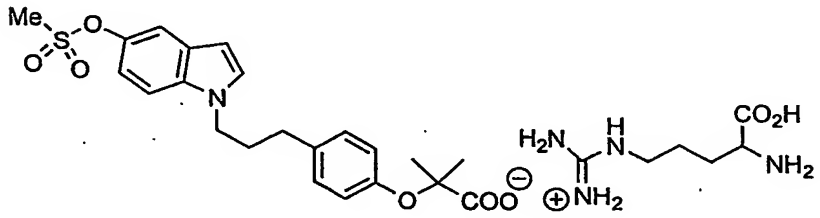
Mp: 134-136 °C.

Example 56
2-methyl-2- [4-{3-(5-methanesulfonyloxyindol-1-yl) propyloxy} phenoxy] propanoic acid Arginine salt



Mp: 125 °C(dec).

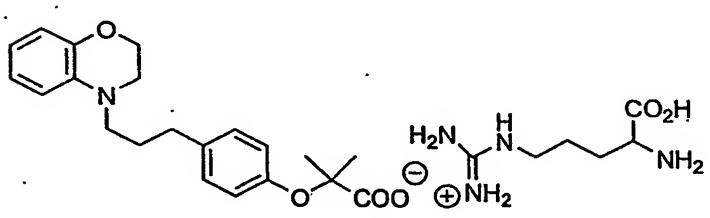
Example 57
2-methyl-2- [4-{3-(5-methanesulfonyloxyindol-1-yl) propyl} phenoxy] propanoic acid Arginine salt



Mp: 80 °C(dec).

Mass m/z (ES): 606 [M+1].

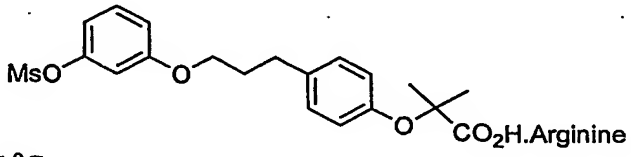
Example 58
2-methyl-2- [4-{3-(3,4-dihydro-2H-bezo [b][1,4] 0xazin-4-yl) propyl} phenoxy] propanoic acid Arginine salt



Mp: 78 °C (dec).

Example 59

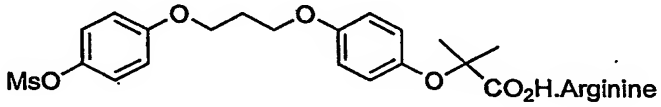
2-Methyl-2-[4-{3-(3-methanesulfonyloxyphenoxy)propyl}phenoxy]propanoic acid Arginine salt



Mp: 95-97 °C.

Example 60

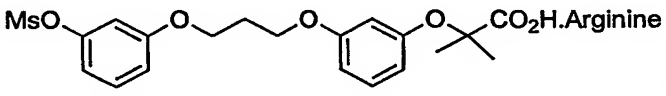
2-Methyl-2-[4-{3-(4-methanesulfonyloxyphenoxy)propyloxy}phenoxy]propanoic acid Arginine salt



Mp: 82-84 °C.
Mass m/z (ES): 599 [M+1].

Example 61

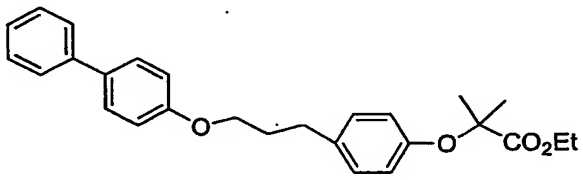
2-Methyl-2-[3-{3-(3-methanesulfonyloxyphenoxy)propyloxy}phenoxy]propanoic acid Arginine salt



M. p: 110-112 °C.

Example 62

Ethyl 2-{4-[3-(biphenyl-4-yloxy)-propyl]-phenoxy}-2-methyl-propanoate

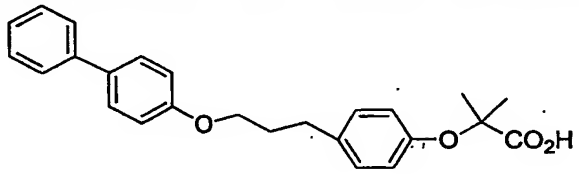


To 4-phenylphenol (400mg, 2.35mmol) dissolved in DMF (10mL) was added K_2CO_3 (973mg, 7.05mmol) and stirred at room temperature for 15min. and then was added ethyl-2-[4-(3-methanesulphonyloxy-propyl)-phenoxy]-2-methyl-propanoate (808mg, 2.35mmol) (obtained in preparation 23) in DMF(5mL) and the mixture was stirred at 80^{0}C for 12h and the mixture was cooled to RT and filtered off, washed the K_2CO_3 cake with ethyl acetate (100mL) the combined filtrates were washed with water thrice and then with brine, dried over Na_2SO_4 and evaporated the ethyl acetate to get a crude product which was purified on silica gel column by eluting with 20%ethyl acetate and hexane to give a thick gum of ethyl 2-{4-[3-(biphenyl-4-yloxy)-propyl]-phenoxy}-2-methyl-propanoate (450 mg, 46%).

^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.60-7.20 (m, 7H), 7.08 (d, J=8.55Hz, 2H), 6.95 (d, J=8.78Hz, 2H), 6.78 (d, J=8.55Hz, 2H), 4.23 (q, J=7.08Hz, 2H), 3.98 (t, J=6.11Hz, 2H), 2.76 (t, J=7.08Hz, 2H), 2.20-2.00 (m, 2H), 1.16 (s,6H), 1.28 (t, J=7.08Hz, 3H).

Example 63

2-{4-[3-(Biphenyl-4-yloxy)-propyl]-phenoxy}-2-methyl-propanoic acid



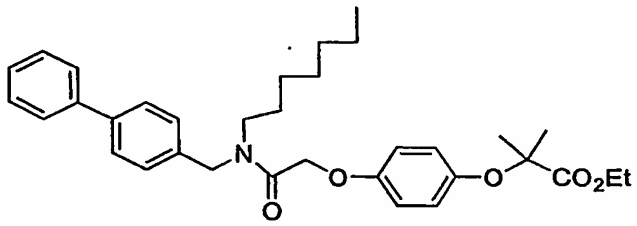
Ethyl 2-{4-[3-(biphenyl-4-yloxy)-propyl]-phenoxy}-2-methyl-propanoate obtained in example 62 was hydrolyzed with aqueous LiOH at 25 °C for 12 h in methanol. THF mixture (3 mL+2 mL) after the completion of reaction the solvent was evaporated and the aqueous layer was washed once with ether and the aqueous layer was acidified with 2 N HCl to pH 2 and extracted with EtOAc and the organic layer was dried with Na_2SO_4 and evaporated under reduced pressure to give 2-{4-[3-(biphenyl-4-yloxy)-propyl]-phenoxy}-2-methyl-propanoic acid (83%).

M.P: 130-133^{0}C;

^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.55-7.29 (m, 7H), 7.13 (d, J=8.60Hz, 2H), 6.95 (d, J=8.59Hz, 2H), 6.88 (d, J=8.60Hz, 2H), 3.99 (t, J=6.18Hz, 2H), 2.79 (t, J=7.30Hz, 2H), 2.13-2.00 (m, 2H), 1.60 (s, 6H).

Example 64

Ethyl 2-{4-[(biphenyl-4-yl methyl-heptyl-carbamoyl)-methoxy]phenoxy}-2-methyl propanoate

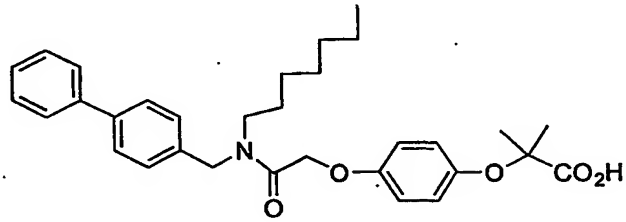


To the ethyl-4-hydroxyphenoxy-2-methyl-propanoate (343mg, 1.53mmol), in dry DMF (10mL) was added K_2CO_3 (575mg, 4.17mmol) and stirred at room temperature for 15 min, to this was added N-biphenyl-4-yl-methyl-2-chloro-N-heptyl-acetamide (500mg, 1.39mmol) (obtained in preparation 24), and stirred at 80^0C for 12h, filtered off the potassium carbonate and diluted with 200ml of ethyl acetate, washed with water, brine, dried over Na_2SO_4 evaporated the organic layer to get a crude product, which was purified on silica gel column to get a pure ethyl-2-{4-[(biphenyl-4-yl methyl-heptyl-carbamoyl)-methoxy]phenoxy}-2-methyl propanoate as a yellow solid (450mg, 60%).

^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.60-7.20 (m, 9H), 6.85 (bs, 4H), 4.73 (s,2H), 4.65 (s, 2H), 2.02 (q, J=7.08Hz, 2H), 3.38 (t, J=7.32Hz, 2H), 1.52 (s, 3H), 1.54 (s, 3H), 1.35-1.15 (m, 10H), 0.87-1.0 (m, 6H).

Example 65

2-{4-[(Biphenyl-4-yl methyl-heptyl-carbamoyl)-methoxy]phenoxy}-2-methyl propanoic acid

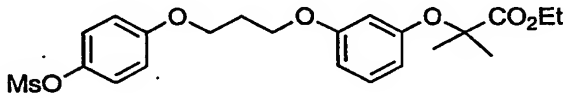


Ethyl-2-{4-[(biphenyl-4-yl methyl-heptyl-carbamoyl)-methoxy]phenoxy}-2-methyl propanoate obtained in example 64 was hydrolysed as given in example 63 with aq LiOH and MeOH : THF mixture to get the title compound (120mg, 30%) as a cream colored solid.

M.P: 142-144^{0}C.

^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.60-7.20 (m, 9H), 6.87 (d, J=9.03Hz, 2H), 6.77 (d, J=9.03Hz, 2H), 4.75 (s, 2H), 4.66 (s, 2H), 3.40 (t, J=7.81Hz, 2H), 1.54 (s, 3H), 1.51 (s, 3H), 1.35-1.10 (m, 10H), 0.87 (t, J=6.10Hz, 3H).

Example 66
Ethyl 2-methyl-2-[3-{3-(4-methanesulfonyloxyphenoxy)propyloxy}phenoxy]propanoate



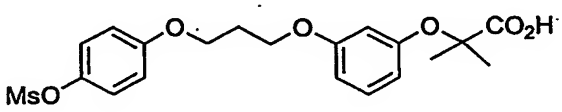
Obtained by following procedure of example 18
Yield: 357 mg, 49%

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.23 (t, J=7.2 Hz, 3H); 1.59(s, 6H); 2.23 (quintet, J= 6 Hz, 2H); 3.10 (s, 3H); 4.10 (t, J=6 Hz, 2H); 4.13 (t, J= 6 Hz, 2H); 4.23 (q, J=7.2 Hz, 2H); 6.38-6.41 (aromatics, 1H); 6.44-6.45 (aromatics, 1H); 6.53-6.56 (aromatics, 1H);6.91 (d, J=9.2 Hz, 2H); 7.11 (t, J= 8.4 Hz, 1H); 7.19 (d, J=9.2 Hz, 2H).

IR (neat) cm^{-1}: 2938, 1731, 1597, 1502.

Mass m/z (CI): 453 [M+1]

Example 67
2-Methyl-2-[3-{3-(4-methanesulfonyloxyphenoxy)propyloxy}phenoxy]propanoic acid



Obtained by following procedure of example 23

Yield: 120 mg, 36 %.

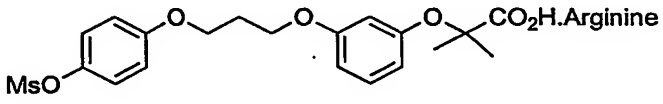
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.60 (s, 6H); 2.24 (quintet, J=6 Hz, 2H); 3.10 (s, 3H); 4.11 (t, J=6 Hz, 2H); 4.14 (t, J=6.2 Hz, 2H); 6.51-6.53 (aromatics, 2H); 6.62-6.65 (aromatics, 1H); 6.91 (d, J=9.1 Hz, 2H); 7.16-7.20 (aromatics, 3H)

IR (neat) cm^{-1}: 2937, 1717, 1596, 1502.

Mass m/z (ES): 425.1 [M+1], 442.3 [M+18], 866.5 [M_2 + 18].

Example 68

2-Methyl-2-[3-{3-(4-methanesulfonyloxyphenoxy)propyloxy}phenoxy]propanoic acid Arginine salt



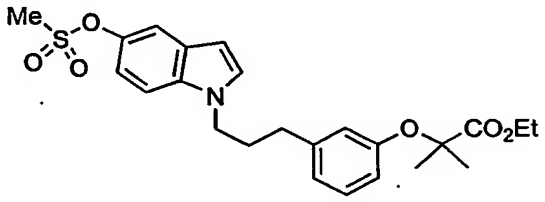
Obtained by following procedure of example 45

Mp: 88-90 °C.

Mass m/z (ES): 599.5 [M+1].

Example 69

Ethyl 2-methyl-2- [3-{3-(5-methanesulfonyloxyindol-1-yl) propyl} phenoxy] propanoate



Obtained by following procedure of example 18

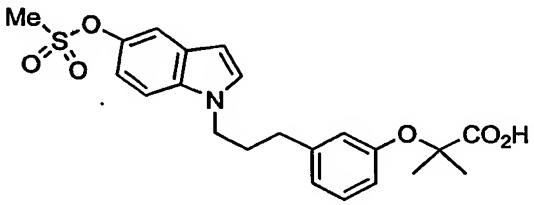
Thick liquid. Yield: 600 mg (83 %).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.22 (t, J=7.2 Hz, 3H); 1.59 (s, 6H); 2.15 (quintet, J=7.2 Hz, 2H); 2.58 (t, J=7.2 Hz, 2H); 3.12 (s, 3H); 4.11 (t, J=7.2 Hz, 2H); 4.21 (q, J=7.2 Hz, 2H); 6.51 (d, J=2.8 Hz, 1H); 6.66-6.70 (aromatics,, 2H); 6.78 (d, J=7.6 Hz, 1H); 7.10-7.24 (aromatics, 4H); 7.53 (d, J=2.4 Hz, 1H).

IR (Neat, cm^{-1}): 2935, 1731, 1583, 1363.

Mass m/z (CI): 460 [M+1].

Example 70
2-methyl-2- [3-{3-(5-methanesulfonyloxyindol-1-yl) propyl} phenoxy] propanoic acid



Obtained by following procedure of example 23

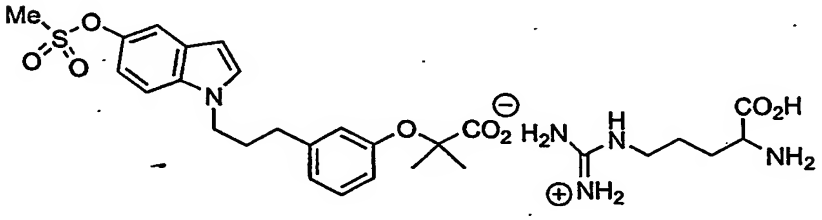
Thick liquid. Yield: 331 mg (67 %).

^1H NMR ($CDCl_3$, 400 MHz) δ: 1.58 (s, 6H); 2.15 (quintet, J=7.2 Hz, 2H); 2.56 (t, J=7.6 Hz, 2H); 3.12 (s, 3H); 4.11 (t, J=7.2 Hz, 2H); 6.51 (d, J=3.2 Hz, 1H); 6.73 (s, 1H); 6.74-6.79 (aromatic, 1H); 6.86 (d, J=7.6 Hz, 1H); 7.10-7.24 (aromatics, 4H); 7.52 (d, J=2.4 Hz, 1H).

IR (Neat, cm^{-1}): 3362, 2937, 1717, 1362.

Mass m/z (ES): 432.3 [M+1], 449.4 [$M+NH_4^+$], 453.3 [$M+Na^+$], 880.5 [$M_2+NH_4^+$].

Example 71
2-methyl-2- [3-{3-(5-methanesulfonyloxyindol-1-yl) propyl} phenoxy] propanoic acid Arginine salt



Obtained by following procedure of example 45

Mp: 85-87 °C (dec).

Mass m/z (ES): 606 [M+1].

The compounds of the present invention lower random blood sugar level, triglyceride, total cholesterol, LDL, VLDL and increase HDL. This may be demonstrated by *in vitro* as well as *in vivo* animal experiments.

Demonstration of Efficacy of Compounds

A) ***In vitro*** **:**

a) Determination of hPPARα activity

Ligand binding domain of hPPARα was fused to A binding domain of Yeast transcription factor GAL4 in eucaryotic expression vector. Using superfect (Qiagen, Germany) as transfecting reagent HEK-293 cells are transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound can be added at different concentrations after 42 hrs of transfection and incubated overnight. Luciferase activity as a function of compound binding/activation capacity of PPARα will be measured using Packard Luclite kit (Packard, USA) in Top Count (Ivan Sadowski, Brendan Bell, Peter Broag and Melvyn Hollis. Gene. 1992. 118 : 137 –141; Superfect Transfection Reagent Handbook. February 1997. Qiagen, Germany).

b) Determination of hPPARγ activity

Ligand binding domain of hPPARγ1 is fused to DNA binding domain of Yeast transcription factor GAL4 in eucaryotic expression vector. Using lipofectamine (Gibco BRL, USA) as transfecting reagent HEK-293 cells are transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound can be added at 1 μM concentration after 48 hrs of transfection and incubated overnight. Luciferase activity as a function of drug binding/activation capacity of PPARγ1 will be measured using Packard Luclite kit (Packard, USA) in Packard Top Count (Ivan Sadowski, Brendan Bell, Peter Broag and Melvyn Hollis. Gene. 1992. 118 : 137 –141; Guide to Eukaryotic Transfections with Cationic Lipid Reagents. Life Technologies, GIBCO BRL, USA).

c) Determination of HMG CoA reductase inhibition activity

Liver microsome bound reductase is prepared from 2% cholestyramine fed rats at mid-dark cycle. Spectrophotometric assays are carried out in 100 mM KH_2PO_4, 4 mM DTT, 0.2 mM NADPH, 0.3 mM HMG CoA and 125 μg of liver microsomal enzyme. Total reaction mixture volume was kept as 1 ml. Reaction was started by addition of HMG CoA. Reaction mixture is incubated at 37 °C for 30 min and decrease in absorbance at 340 nm was recorded. Reaction mixture without substrate was used as blank (Goldstein, J. L and Brown, M. S. Progress in understanding the LDL receptor and HMG CoA reductase, two membrane proteins that regulate the plasma cholesterol. J. Lipid Res. 1984, 25: 1450 – 1461). The test compounds will inhibited the HMG CoA reductase enzyme.

In vivo

a) Efficacy in genetic models

Mutation in colonies of laboratory animals and different sensitivities to dietary regimens have made the development of animal models with non-insulin dependent diabetes and hyperlipidemia associated with obesity and insulin resistance possible. Genetic models such as db/db and ob/ob (Diabetes, (1982) 31(1) : 1- 6) mice and zucker fa/fa rats have been developed by the various laboratories for understanding the pathophysiology of disease and testing the efficacy of new antidiabetic compounds (Diabetes, (1983) 32: 830-838 ; Annu. Rep. Sankyo Res. Lab. (1994). 46 : 1-57). The homozygous animals, C57 BL/KsJ-db/db mice developed by Jackson Laboratory, US, are obese, hyperglycemic, hyperinsulinemic and insulin resistant (J. Clin. Invest., (1990) 85 : 962-967), whereas heterozygous are lean and normoglycemic. In db/db model, mouse progressively develops insulinopenia with age, a feature commonly observed in late stages of human type II diabetes when blood sugar levels are insufficiently controlled. The state of pancreas and its course vary according to the models. Since this model resembles that of type II diabetes mellitus, the compounds of the present invention will be tested for blood sugar and triglycerides lowering activities.

Male C57BL/KsJ-db/db mice of 8 to 14 weeks age, having body weight range of 35 to 60 grams, bred at Dr. Reddy's Research Foundation (DRF) animal house, were used in the experiment. The mice are provided with standard feed (National Institute of Nutrition (NIN), Hyderabad, India) and acidified water, ad libitum. The

animals having more than 350 mg / dl blood sugar will be used for testing. The number of animals in each group will be 4.

Test compounds are suspended on 0.25 % carboxymethyl cellulose and administered to test group at a dose of 0.1 mg to 30 mg / kg through oral gavage daily for 6 days. The control group receives vehicle (dose 10 ml / kg). On 6th day the blood samples will be collected one hour after administration of test compounds / vehicle for assessing the biological activity.

The random blood sugar and triglyceride levels can be measured by collecting blood (100 µl) through orbital sinus, using heparinised capillary in tubes containing EDTA which was centrifuged to obtain plasma. The plasma glucose and triglyceride levels can be measured spectrometrically, by glucose oxidase and glycerol-3-PO_4 oxidase/peroxidase enzyme (Dr. Reddy's Lab. Diagnostic Division Kits, Hyderabad, India) methods respectively.

The blood sugar and triglycerides lowering activities of the test compound are calculated according to the formula.

The ob/ob mice were obtained at 5 weeks of age from Bomholtgard, Denmark and were used at 8 weeks of age. Zucker fa/fa fatty rats are obtained from IffaCredo, France at 10 weeks of age and were used at 13 weeks of age. The animals are maintained under 12 hour light and dark cycle at 25 + 1 °C. Animals are given standard laboratory chow (NIN, Hyderabad, India) and water, *ad libitum* (Fujiwara, T., Yoshioka, S., Yoshioka, T., Ushiyama, I and Horikoshi, H. Characterization of new oral antidiabetic agent CS-045. Studies in KK and ob/ob mice and Zucker fatty rats. Diabetes. 1988. 37 : 1549 – 1558).

The test compounds will be administered at 0.1 to 30 mg/kg/day dose for 9 days. The control animals receives the vehicle (0.25 % carboxymethylcellulose, dose 10 ml/kg) through oral gavage.

The blood samples can be collected in fed state 1 hour after drug administration on 0 and 9 day of treatment. The blood can be collected from the retro-orbital sinus through heparinised capillary in EDTA containing tubes. After centrifugation, plasma sample will be separated for triglyceride, glucose, free fatty acid, total cholesterol and insulin estimations. Measurement of plasma triglyceride, glucose, total cholesterol can be done using commercial kits (Dr. Reddy's Laboratory, Diagnostic Division, India). The plasma free fatty acid will be measured using a

commercial kit from Boehringer Mannheim, Germany. The plasma insulin can be measured using a RIA kit (BARC, India). The reduction of various parameters examined will be calculated according to the formula given below.

In ob/ob mice oral glucose tolerance test is performed after 9 days treatment. Mice are fasted for 5 hrs and challenged with 3 gm/kg of glucose orally. The blood samples are collected at 0, 15, 30, 60 and 120 min for estimation of plasma glucose levels.

b) **Plasma triglyceride and Cholesterol lowering activity in hypercholesterolemic rat models**

Male Sprague Dawley rats (NIN stock) were bred in DRF animal house. Animals were maintained under 12 hour light and dark cycle at 25 ± 1 ^{0}C. Rats of 180 - 200 gram body weight range were used for the experiment. Animals are made hypercholesterolemic by feeding 2% cholesterol and 1% sodium cholate mixed with standard laboratory chow [National Institute of Nutrition (NIN), Hyderabad, India] for 6 days. Throughout the experimental period the animals were maintained on the same diet (Petit, D., Bonnefis, M. T., Rey, C and Infante, R. Effects of ciprofibrate on liver lipids and lipoprotein synthesis in normo- and hyperlipidemic rats. Atherosclerosis. 1988. 74 : 215 – 225).

The test compounds can be administered orally at a dose 0.1 to 30 mg/kg/day for 3 days. Control group was treated with vehicle alone (0.25 % Carboxymethylcellulose; dose 10 ml/kg).

The blood samples can be collected in fed state 1 hour after drug administration on 0 and 3 day of compound treatment. The blood can be collected from the retro-orbital sinus through heparinised capillary in EDTA containing tubes. After centrifugation, plasma sample will be separated for total cholesterol, HDL and triglyceride estimations. Measurement of plasma triglyceride, total cholesterol and HDL are were done using commercial kits (Dr. Reddy's Laboratory, Diagnostic Division, India). LDL and VLDL cholesterol can be calculated from the data obtained for total cholesterol, HDL and triglyceride. The reduction of various parameters examined are calculated according to the formula.

c) **Plasma triglyceride and total cholesterol lowering activity in Swiss albino mice and Guinea pigs**

Male Swiss albino mice (SAM) and male Guinea pigs are obtained from NIN and housed in DRF animal house. All these animals are maintained under 12 hour light and dark cycle at 25 ± 1 ^{0}C. Animals are given standard laboratory chow (NIN, Hyderabad, India) and water, *ad libitum*. SAM of 20 - 25 g body weight range and Guinea pigs of 500 - 700 g body weight range are used (Oliver, P., Plancke, M. O., Marzin, D., Clavey, V., Sauzieres, J and Fruchart, J. C. Effects of fenofibrate, gemfibrozil and nicotinic acid on plasma lipoprotein levels in normal and hyperlipidemic mice. Atherosclerosis. 1988. 70 : 107 – 114).

The test compounds can be administered orally to Swiss albino mice at 0.3 to 30 mg/kg/day dose for 6 days. Control mice are treated with vehicle (0.25% Carboxymethylcellulose; dose 10 ml/kg). The test compounds are administered orally to Guinea pigs at 0.3 to 30 mg/kg/day dose for 6 days. Control animals are treated with vehicle (0.25% Carboxymethylcellulose; dose 5 ml/kg).

The blood samples can be collected in fed state 1 hour after drug administration on 0 and 6 day of treatment. The blood can be collected from the retro-orbital sinus through heparinised capillary in EDTA containing tubes. After centrifugation, plasma sample was separated for triglyceride and total cholesterol (Wieland, O. Methods of Enzymatic analysis. Bergermeyer, H. O., Ed., 1963. 211 - 214; Trinder, P. Ann. Clin. Biochem. 1969. 6 : 24 – 27). Measurement of plasma triglyceride, total cholesterol and HDL are done using commercial kits (Dr. Reddy's Diagnostic Division, Hyderabad, India).

d) **Body weight reducing effect in cholesterol fed hamsters :**

Male Syrian Hamsters are procured from NIN, Hyderabad, India. Animals are housed at DRF animal house under 12 hour light and dark cycle at 25 ± 1 ^{0}C with free access to food and water. Animals are maintained with 1 % cholesterol containing standard laboratory chow (NIN) from the day of treatment.

The test compounds can be administered orally at 1 to 30 mg/kg/day dose for 15 days. Control group animals are treated with vehicle (Mill Q water, dose 10 ml/kg/day). Body weights are measured on every 3rd day.

Formulae for calculation :

1. Percent reduction in Blood sugar / triglycerides / total cholesterol will be calculated according to the formula :

$$\text{Percent reduction (\%)} = \left[1 - \frac{TT / OT}{TC / OC}\right] \text{ X } 100$$

OC = Zero day control group value

OT = Zero day treated group value

TC = Test day control group value

TT = Test day treated group value

2. LDL and VLDL cholesterol levels will be calculated according to the formula :

$$\text{LDL cholesterol in mg/dl} = [\text{ Total cholesterol - HDL cholesterol - } \frac{\text{Triglyceride}}{5}] \text{ mg/dl}$$

VLDL cholesterol in mg/dl=[Total cholesterol-HDL cholesterol-LDL cholesterol] mg/dl.

We Claim:

1. A compound of formula 1

$$Ar\text{-}I\text{——}Y\text{——}Ar\text{-}II\text{——}Z \qquad (1)$$

wherein Ar-I represents a monocyclic or polycyclic aromatic or non aromatic ring or partly saturated aromatic polycyclic, which may optionally contain up to 3 heteroatoms selected from N, S, or O. The said monocyclic or polycyclic ring may be unsubstituted or have up to 4 substituents which may be identical or different;

Ar-II represents a monocyclic or bicylic or partly saturated aromatic bicyclic aromatic ring which may optionally contain upto 3 heteroatoms selected from N, S or O. The aromatic ring may be unsubstituted or have up to 4 substituents which may be identical or different;

Z represents $(CH_2)oACR^7R^8(CH_2)_pW$, where o and p are each independently an integer from 0 to 4;

A represents O, S, NR^1 or a direct bond;

W represents CO_2R^9 or $CONR^1R^2$;

The substituents on Ar-I and Ar-II are selected from halogen, C_{1-10} alkyl, hydroxy, hydroxy C_{1-6} alkyl, C_{1-10} alkoxy, nitro, cyano, oxo, aryl, arylalkyl, alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, aryloxy, arylalkoxy, alkylcarbonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, arylalkoxycarbonylamino, fluorenylmethoxycarbonyl (Fmoc), fluorenylmethoxycarbonylamino (N-Fmoc), $-NR^1R^2$, $-OCONR^1R^2$, NR^1COOR^2, $-NR^1COR^2$, $-NR^1SO_2R^2$, $NR^1CONR^1R^2$, $-NR^2CSNR^1R^2$, SO_2R^3, OSO_2R^3, SO_2OR^3, $-SOR^3$, $-SO_2NR^1R^2$, $-COOR^4$, $-COR^4$, $-CONR^1R^2$, C_{1-10} alkylthio, thio C_{1-10} alkyl;

Y is selected from $(CH_2)_m$, $(CH_2)_mB(CH_2)_n$, $(CH_2)_mC(O)NR^5(CH_2)_n$, $(CH_2)_mNR^5C(O)(CH_2)_n$, $(CH_2)_mNR^5C(O)NR^5(CH_2)_n$, $(CH_2)_mNR^5C(O)O(CH_2)_n$, $(CH_2)_mNR^5C(O)(CH_2)_nO$, $(CH_2)_mNR^5OC(O)(CH_2)_n$, $(CH_2)_mCR^5CR^6(CH_2)_n$, $(CH_2)_mCR^5{=}CR^6(CH_2)_n$, $(CH_2)_mCR^5{\equiv}CR^6(CH_2)_n$, $(CH_2)_mOC(O)(CH_2)_n$, $(CH_2)_mC(O)O(CH_2)_n$, $(CH_2)_lB(CH_2)_mB(CH_2)_n$, where m and n are each independently an integer from 0 to 4; B may identical or different and represent S, O or NR^5 with a proviso that when Y has more than one heteroatom, no two heteroatoms are adjacent to each other.

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are each independently selected from hydrogen, halogen, hydroxy, hydroxy C_{1-10}alkyl, C_{1-10}alkyl, aryl, aroyl, aryl C_{1-10}alkyl, amino,

amino C_{1-10} alkyl, acylamino, acylaminoC_{1-10}alkyl, C_{1-10}alkoxy, C_{1-10}alkoxyC_{1-10}alkyl, cycloalkyl, heterocyclyl, C_{1-10}alkoxycarbonyl, aryloxycarbonyl, C_{1-10}alkylaminocarbonyl, arylaminocarbonyl groups; optionally, either of R^8 or R^9 may form a bond with Ar-II.

in all their stereoisomeric forms and mixtures thereof in any ratio and pharmaceutically acceptable salts thereof;

2. A pharmaceutical composition, which comprises an effective amount of a compound of formula (1),

Ar-I—Y—Ar-II—Z (1)

as defined in claim 1 and a pharmaceutically acceptable carrier, diluent, excipient or a solvate.

3. A pharmaceutical composition, which comprises an effective amount of a compound of formula (1), as defined in claim 1 in combination with a HMG CoA reductase inhibitor; cholesterol absorption inhibitor; antiobesity drug; lipoprotein disorder treatment drug: fibrate; hypoglycemic agent: insulin; biguanide; sulfonylurea; thiazolidinedione; dual PPARα and γ agonist or a mixture thereof and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

4. A method for improving insulin sensitivity which would eventually lead to treatment / prophylaxis of disorders like, but not limited to, non insulin dependent diabetes mellitus, obesity, dyslipidemia, atherosclerosis to a patient in need of, which comprises administering to the said patient a therapeutically effective amount of the compound of formula 1 as claimed in claim 1 either alone or in combination with HMG CoA reductase inhibitor; cholesterol absorption inhibitor; antiobesity drug; lipoprotein disorder treatment drug: fibrate; hypoglycemic agent: insulin; biguanide; sulfonylurea; thiazolidinedione; dual PPARα and γ agonist or a mixture thereof.

Dated this twenty first (21st) day of October 2003

R Rajagopalan

Dr. R. Rajagopalan
for Dr. Reddy's Laboratories Ltd.